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ASSOCIATED MOVEMENTS IN THE OCULOMOTOR AND FACIAL MUSCLES

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ABNORMAL motor phenomena belonging—generally speaking—to the vast group of hyperkineses do occur in the oculomotor muscles after incomplete recovery from a third nerve palsy. They constitute, as Bielschowsky [1] rightly said, "a problem of great biologic interest." But this difficult and fascinating problem has been much neglected in the neurologic literature. The symptomatology and pathogenesis of abnormal motor phenomena in the facial muscles after incomplete recovery from facial nerve palsy have been widely discussed by neurologists. But there is little in the neurologic literature on the subject of similar movements after oculomotor palsy. To Dejerine [2] it seemed that abnormal movements occur only after a seventh nerve palsy, and in no other instance. Leading contemporary neurologists, such as Harris [3] and Kramer,[4] have expressed the same view. The latter said: "It is remarkable that contractures and associated movements are observed in the region of the facial nerve and not in the region of any other nerve." Oppenheim,[5] in his textbook, devotes but four lines, in small print, to the subject of abnormal movements following a third nerve palsy. No mention is made of this subject in the textbooks of Wilson, Brain, Grinker, Wechsler, Nielsen, Bing and others, nor is it referred to in the most

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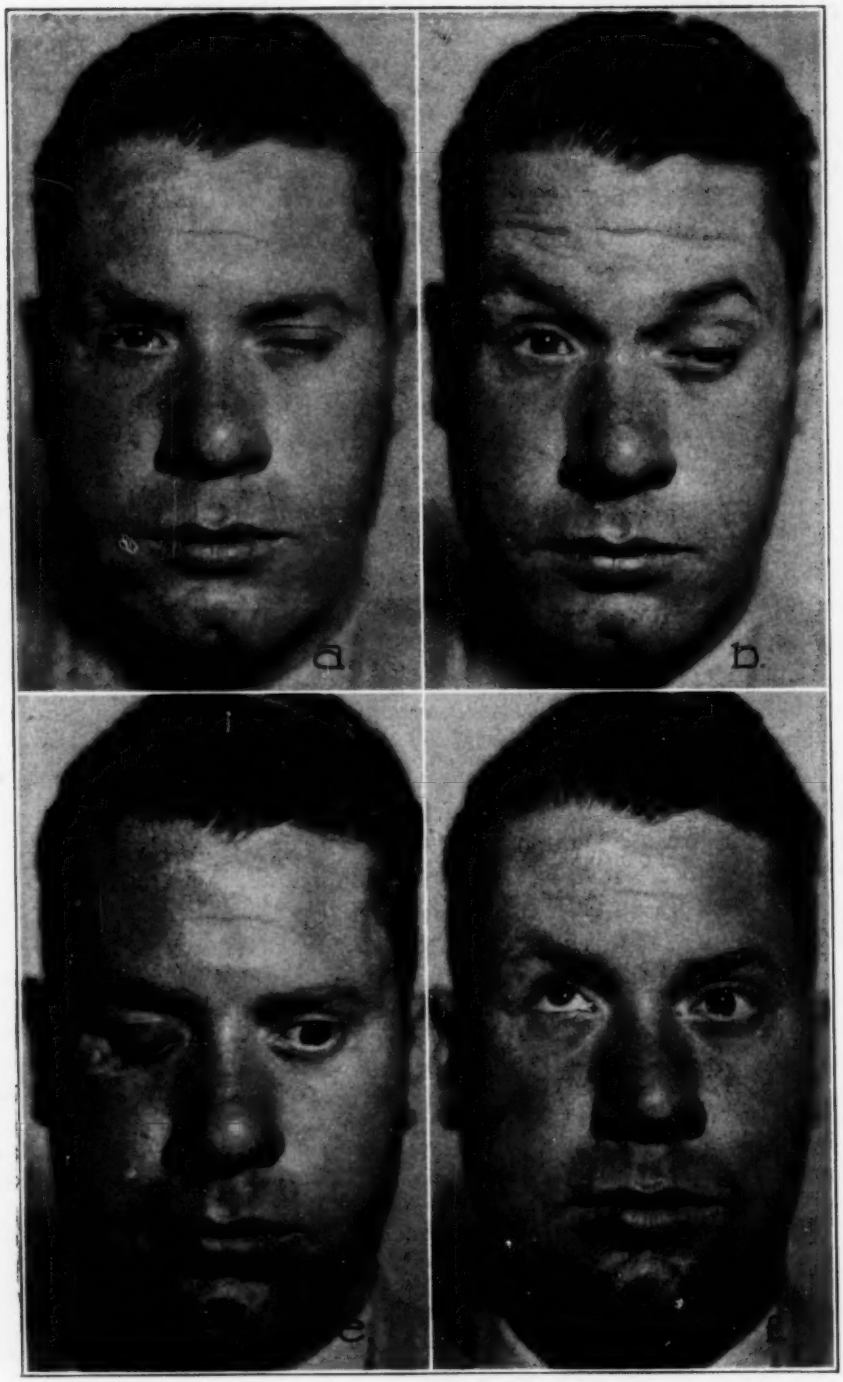
1. Bielschowsky, A.: Die Motilitätsstörungen der Augen, in Graefe, A., and Saemisch, T.: Handbuch der gesamten Augenheilkunde, ed. 2, Leipzig, Wilhelm Engelmann, 1910, vol. 8, pt. 2, chap. 9, p. 196.

2. Dejerine, J.: Sémiologie des affections du système nerveux, Paris, Masson & Cie, 1926, p. 583.

3. Harris, W.: Neuritis and Neuralgia, London, Oxford University Press, 1926, p. 364; Tremor, Ataxy and Spasm, Lancet **2**:1145, 1934.

4. Kramer, F., in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1936, vol. 4, p. 350.

5. Oppenheim, H.: Lehrbuch der Nervenkrankheiten, ed. 7, Berlin, S. Karger, 1923, p. 737.



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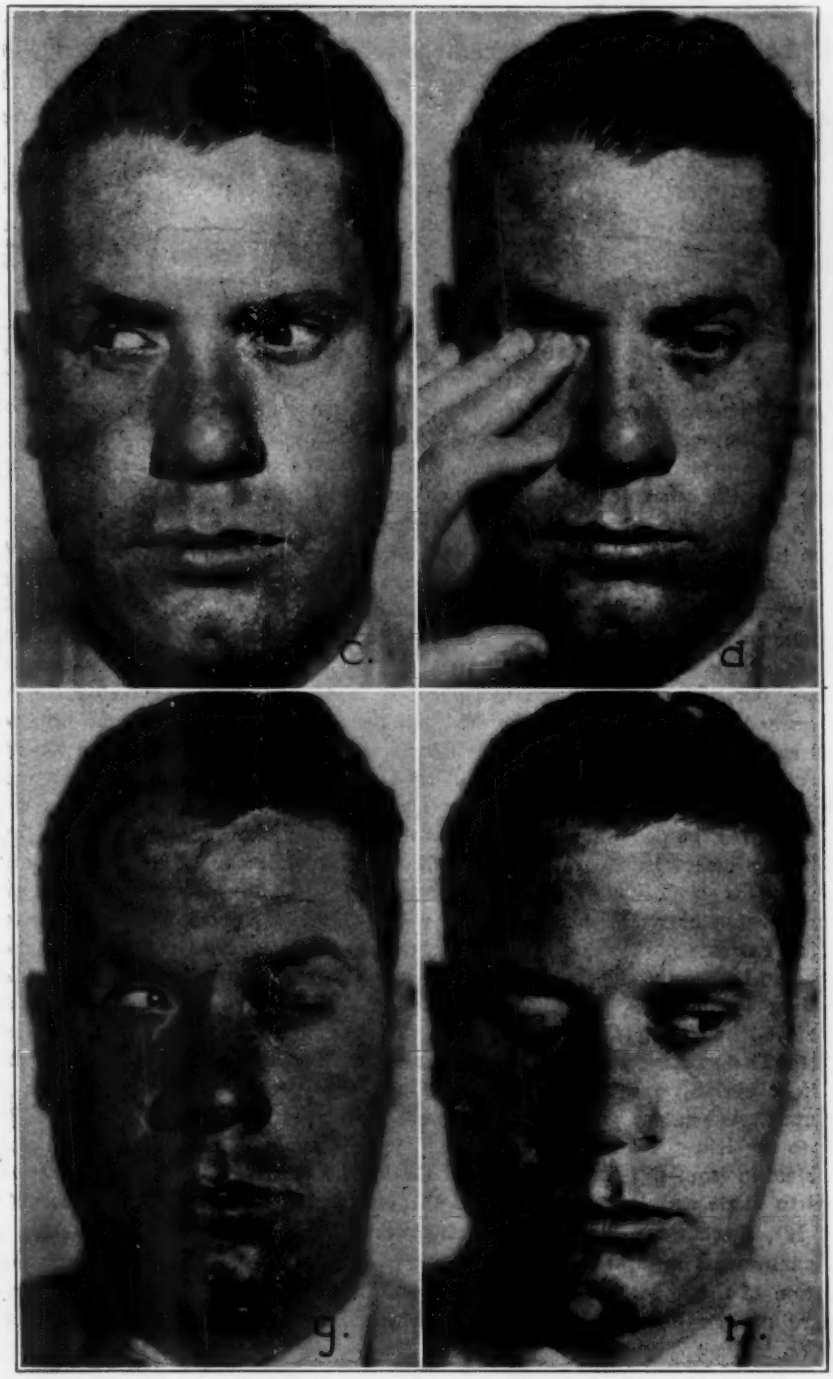


Fig. 1 (case 1).—Patient (*a*) looking straight ahead, (*b*) trying to open his eyes wide, (*c*) looking to the right, (*d*) with the right eye passively closed, (*e*) looking downward, (*f*) looking upward, (*g*) looking horizontally to the left, (*h*) looking to the left and downward.

extensive treatise on neurologic examination in existence, that of Sahli. Ophthalmologists have written extensively on this subject, but their work is predominantly descriptive. They have developed a hypothesis on the pathogenesis of these phenomena which has been widely accepted also by neurologists.

The primary object of the present study is a critical analysis of this hypothesis, based on the personal observation of 4 cases.

REPORT OF CASES

CASE 1.—A man aged 23 sustained a skull fracture and severe injury to the brain in an automobile accident. He underwent four neurologic examinations, twenty-one, thirty, thirty-seven and forty-five months, respectively, after the accident. The same condition was found each time, namely, left-sided oculomotor palsy, as the only sequela of the injury. There were no other neurologic changes. He had no postcommotional cerebral syndrome, no double vision. His only complaint was the cosmetic effect of his oculomotor palsy.

On examination he showed an incomplete palsy of the left oculomotor nerve. From his statement it was concluded that this palsy had been complete after the injury and had slowly improved. The left eye was in abduction of about 20 degrees. The upward and downward movements of the eye were greatly limited. The adduction was slightly better, and the abduction was normal. The left pupil was twice the size of the right and showed no reaction to light and no reaction on inward, outward or downward movement of the eye, but it contracted slightly on upward movement. No consensual pupillary reaction to light was obtained from right to left, but it was present from left to right. When he looked straight ahead (fig. 1*a*), pronounced ptosis and an abducent position of the left eye were noted. The orbicularis oculi muscle was normal. When asked to open his eyes wide (fig. 1*b*), he performed the movement hesitatingly, and despite maximal effort and strong innervation of the frontal muscle he was able to lift his left lid only slightly; the eyeball moved simultaneously very slightly inward or remained immobile. On his looking to the right (fig. 1*c*), the left eyeball did not assume the full extreme position, as did the right. The left upper lid rose and assumed a position higher than the right one. When the patient looked straight ahead with the right eye passively closed by the fingers of the examiner (fig. 1*d*), the left eye moved inward, and the left lid rose. It rose higher the more he fixated an object. The moment the examiner removed his fingers and the patient opened his right eye, his left lid again drooped and the eyeball assumed a position of abduction. When, with his right eye passively closed, the patient was asked to look to the left, the left lid drooped; and it rose again when the patient fixated an object in front of him. No lifting of the left lid occurred when the patient was asked to fixate a distant object with both eyes open. When he looked downward (fig. 1*e*), there were a very slight downward movement of the left eyeball, a slight movement inward, a distinct rotation of the eye clockwise and a conspicuous elevation of the upper lid. When he looked upward (fig. 1*f*), there were a slight upward movement of the eyeball, a pronounced inward movement—much more than on looking downward—and a marked elevation of the upper lid. When the patient looked horizontally to the left, the ptosis of the left lid became complete (fig. 1*g*); but when he looked to the left and downward, the left upper lid rose automatically (fig. 1*h*). On his looking to the left and upward, the eye remained in the same horizontal position, and the ptosis remained as in the position of rest.

On strong convergence a slight inward movement of the left eye occurred, with elevation of the left lid, but both movements were less marked than when he was asked to move the left eye inward. On closing of the eye, Bell's phenomenon was present on both sides.

CASE 2.—A 7 year old boy fell thirty-five days previous to the neurologic examination and suffered a fracture of the occipital bone; two days later pneumococcic meningitis developed. After two more days left-sided palsy of the

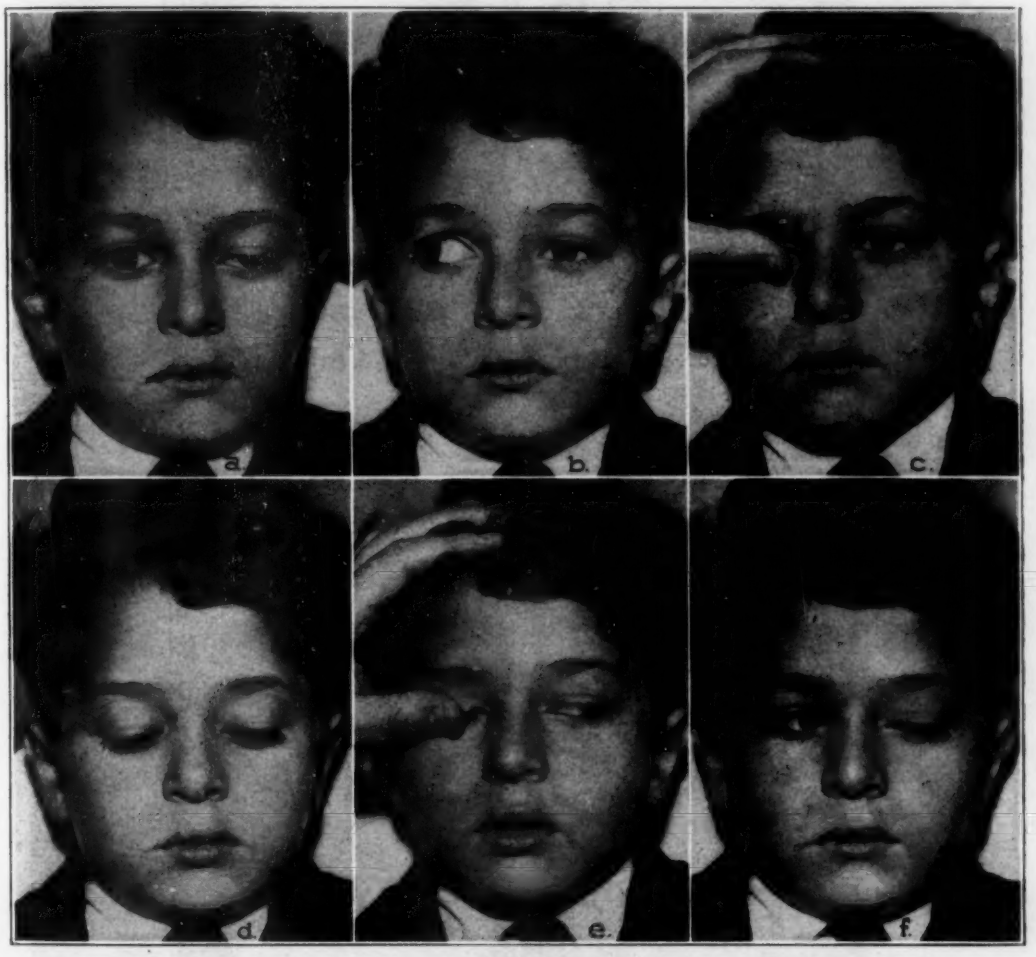
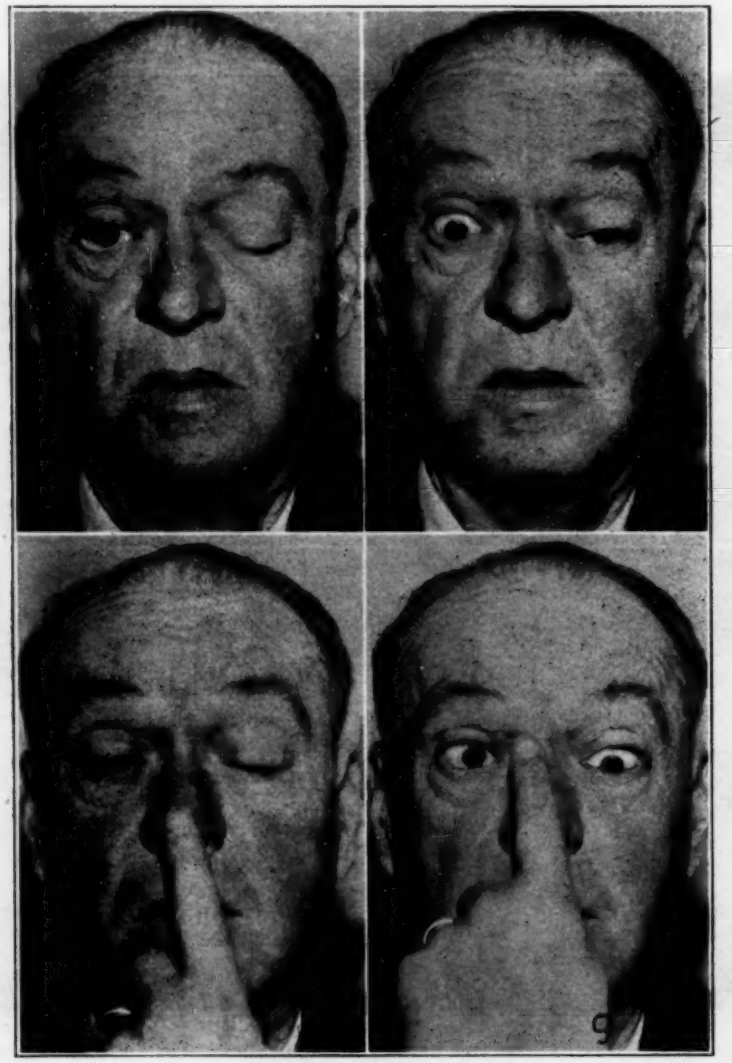


Fig. 2 (case 2).—Patient (*a*) looking straight ahead, (*b*) looking to the right, (*c*) with the right eye passively closed, (*d*) looking downward, (*e*) with the right eye passively closed, looking to the left, (*f*) looking horizontally to the left.

third nerve with complete ptosis was noticed. He had no complaints referable to the cerebral injury, and the neuropathologic changes were confined to the left oculomotor nerve. The patient showed an incomplete left-sided palsy of the third nerve, with mild ptosis and an abducent position of the eye (fig. 2 *a*). Voluntarily, on great effort, he was able to lift the upper left lid slightly. The pupils were normal. On his looking to the right (fig. 2 *b*), the left eyeball followed only as far

as the midline and the left lid rose but not so high as the right. When the right eye was passively closed by the fingers of the examiner, the left eyeball moved inward and the left eyelid upward (fig. 2 *c*). On his looking downward (fig. 2 *d*), the left upper lid moved downward in a normal fashion. When, with the right eye remaining passively closed, the patient was asked to look to the left, there



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was no elevation of the upper left lid, and the ptosis remained as it was in the position of rest (fig. 2 *e*). On his looking horizontally to the left, the ptosis became more marked (fig. 2 *f*). After one year the patient was reexamined. He showed complete recovery, and no associated movements or any other pathologic changes relative to the left eye could be demonstrated. The recovery took place without any therapy, exercise or other measure.

CASE 3.—A 58 year old man had tabes dorsalis and incomplete paralysis of the left third nerve. The first symptoms of this paralysis dated ten years back. When the patient was at rest and looked straight ahead, the ptosis was complete (fig.3 *a*). On great effort he was able to lift his left eyelid slightly (fig. 3 *b*) but only for a short time. On looking to the right, he demonstrated a partial paralysis of the

Fig. 3 (case 3).—Patient (*a*) looking straight ahead, (*b*) trying to open his eyes wide, (*c*) looking to the right, (*d*) with the right eye passively closed, (*e*) looking downward, (*f*) fixating an object below the horizontal level, (*g*) fixating an object at the horizontal level, (*h*) looking upward, (*i*) looking to the left and horizontally, (*j*) looking to the left and upward.

left rectus internus muscle, and the left eyelid rose automatically to a maximal degree (fig. 3 *c*). When the right eye was passively closed by the finger of the examiner and the patient stared straight ahead, the left eyelid rose (fig.3 *d*). When

he looked downward (fig. 3 *e*) or when he fixated an object below the horizontal level (3 *f*), the left eyelid followed the downward movement of the eye in a normal fashion, even more than did the right eyelid. But when the patient was asked to fixate an object at the horizontal level, the left eyelid rose automatically to a considerable extent (fig. 3 *g*). When he looked upward, the left eye hardly participated but moved slightly inward, while the left eyelid moved extensively upward (fig. 3 *h*). When he was asked to look to the left and horizontally, the ptosis

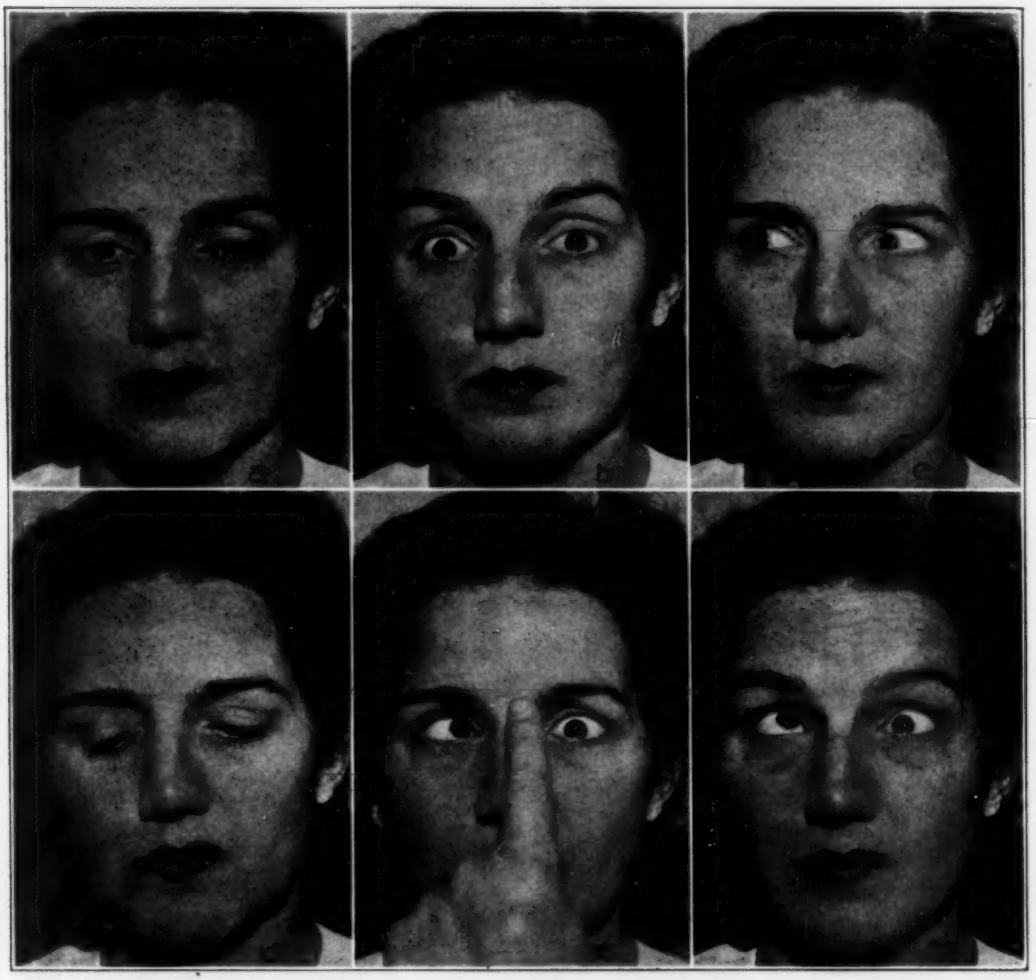

Fig. 4 (case 4).—Patient (*a*) looking straight ahead, (*b*) trying to open the eyes wide, (*c*) looking to the right, (*d*) fixating an object below the horizontal level, (*e*) fixating an object at the horizontal level, (*f*) looking upward.

remained unchanged (fig. 3 *i*); but when he looked to the left and upward (fig. 3 *j*), the left eyeball hardly followed this upward movement, whereas the left eyelid rose automatically.

Case 4.—A 40 year old woman had a specific infection, first diagnosed three years before the present examination. At that time a lesion of the left oculomotor

nerve was noted. At the present examination she showed an incomplete palsy of the left oculomotor nerve with ptosis (fig. 4 *a*). According to her statement, this ptosis was at first complete but since had slowly diminished. On strong exertion she was able to correct this ptosis (fig. 4 *b*) and could lift her left lid, but only for a few seconds. The left lid then moved downward to the former position. When she looked toward the right, there was an automatic elevation of the left upper lid (fig. 4 *c*). There was no elevation of the upper lid on looking downward, the left upper lid following the downward movement of the eyeballs in a normal fashion. No elevation of the upper lid resulted when the patient was asked to fixate an object below the horizontal level (fig. 4 *d*); however, when she was trying to converge on an object placed at the level of the eyes, the left lid rose, although the adduction of the left eye was very deficient (fig. 4 *e*). On looking upward, there was almost no upward movement of the eyeball but, rather, an automatic movement of the eyeball inward with elevation of the upper lid (fig. 4 *f*).

ASSOCIATED MOVEMENTS IN OCULOMOTOR MUSCLES

Retraction of the upper lid on downward movement of the eyeball occurring after incomplete recovery of a third nerve palsy is often called the Fuchs' sign. Fuchs [6] stated in 1917 that he was the first who,[7] in 1893 published such observations, and Coppez [8] agreed with him. This is not correct, since Fuchs in his first paper cited the pertinent observation of Browning,[9] in 1890. It was actually Gowers [10] who, in 1879, described these phenomena for the first time. His illustrations showed convincingly the abnormal retraction of the upper lid on downward movement of the eye, the so-called Fuchs sign.

This phenomenon is often also called the Köppen sign or the Brixa-Köppen sign, in accordance with the publication of Köppen,[11] in 1894, and that of Brixa,[12] in 1897. The most popular designation is the pseudo-Graefe sign, coined by Köppen, since in the original Graefe sign, described for the first time in a case of exophthalmic goiter, the upper lid does not follow the downward movement of the eyeball. It is interesting that Fuchs,[7] in his first publication, of 1893, remarked concerning the phenomenon observed in cases of oculomotor palsy that it reminded one

6. Fuchs, E.: Ueber die pathologische Mitbewegung der Lider, Jahrb. f. Psychiat. u. Neurol. **38**:49, 1917.

7. Fuchs, E.: Assoziation von Lidbewegung mit seitlichen Bewegungen des Auges, Beitr. z. Augenh., 1893, no. 11, p. 12.

8. Coppez, H.: Sur le pseudo-signe de Graefe (signe de Fuchs), Arch. d'opht. **48**:385, 1931.

9. Browning, F. W.: Affections of the Muscular and Nervous Systems, Tr. Ophth. Soc. U. Kingdom **10**:187, 1890.

10. Gowers, W. R.: The Movements of the Eyelids, Med.-Chir. Tr. **62**:429, 1879.

11. Köppen, M.: Beiträge zur pathologischen Anatomie und zum klinischen Symptomencomplex multipler Gehirnerkrankungen, Arch. f. Psychiat. **26**:99, 1894.

12. Brixa: Mitbewegung des Oberlides bei Bewegungen des Augapfels, Beitr. z. Augenh. **26**:52, 1897.

of the von Graefe symptom in exophthalmic goiter. The name pseudo-Graefe sign is objectionable for several reasons. It does not include the phenomenon of elevation of the eyelid on adduction and on elevation of the eyeball. Furthermore, it does not include the phenomenon of dropping of the eyelid on abduction. The name covers only the lifting of the eyelid on looking downward, whereas the most common and the most outstanding movement occurring after incomplete recovery from the third nerve palsy is the elevation of the lid on adduction of the eyeball. There are cases, such as in this series, cases 2 and 3, in which the so-called pseudo-Graefe phenomenon is not shown, but all other phenomena usually associated with it are present. Coppez [8] entitled his paper "the Pseudo-Sign of Graefe (Sign of Fuchs)." This double name can hardly contribute to simplification of the nomenclature.

The phenomenon of involuntary lifting of the ptotic eyelid on passive closing of the normal eye was described in 1893 by de Mello Vianna [13] as *ptosis à bascule* and in 1896 by Paccetti [14] as *ptosi a bilancia.* The latter name found entrance in textbooks (Purves-Stewart [15]) and in the literature (Alessandrini,[16] Caramazza [17]). In the discussion of this phenomenon, Gifford [18] spoke of "paradoxic elevation of the lid"; Yanes,[19] of "paradoxic monocular ptosis." In their classic handbook on the neurology of the eye, Wilbrand and Sänger,[20] in describing this phenomenon, overlooked the intimate association of the adduction of the eye and the lifting of the eyelid, though their illustrations show this clearly. They tried to explain this phenomenon as follows: On exclusion of the normal eye, the full energy of the will is directed toward the frontal muscle of the affected side, a better contraction of which can thus be achieved. However, the legend of one of their illustrations states that the patient was unable to lift the upper lid even when she tried "with the greatest exertion of will."

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13. de Mello Vianna, J.: Recherches cliniques sur les paralysies des muscles de l'œil, Thesis, Paris, no. 417, 1893.

14. Paccetti, G.: Sulle paralisi funzionali dei muscoli oculari, Policlinico (sez. med.) **3**:101, 1896.

15. Purves-Stewart, J.: The Diagnosis of Nervous Diseases, ed. 8, Baltimore, William Wood & Company, 1937, p. 248.

16. Alessandrini, A.: Contributo alla casistica della "ptosi a bilancia," Manicomio **38**:59, 1925.

17. Caramazza, F.: Considerazioni cliniche su di un caso di ptosi a bilancia, Riv. oto-neuro-oftal. **7**:165, 1930.

18. Gifford, S. R.: Paradoxic Elevation of the Lid, Arch. Ophth. **22**:252 (Aug.) 1939.

19. Yanes, T. R.: Paradoxic Monocular Ptosis, Arch. Ophth. **23**:1169 (June) 1940.

20. Wilbrand, H., and Sänger, A.: Die Neurologie des Auges, Wiesbaden, J. F. Bergmann, 1900, vol. 1, p. 77.

To speak of a "spasm" of the levator palpebrae muscle (Galezowski,[21] Bielschowsky[22]) or of "spastic contracture" (Wilbrand and Behr[23]) does not supply an accurate description, nor is it physiologically correct. Spiegel and Sommer[24] described the pseudo-Graefe phenomenon thus: "The paresis of the levator can be transformed in a contracture of this muscle." Other authors speak of "paradoxic movements."

To do physiologic justice to the phenomena that occur after incomplete recovery of a third nerve palsy, it is best to give them the only adequate and physiologically correct name—associated movements. It is, physiologically speaking, an associated movement when the voluntary innervation of the rectus inferior causes a simultaneous, involuntary, automatic, unsuppressible—an associated—innervation of the levator palpebrae superioris.

ASSOCIATED MOVEMENTS IN FACIAL MUSCLES

Observing these associated movements which occur after incomplete recovery from a third nerve palsy, one is struck by the similarity between these movements and those occurring after incomplete recovery from a facial nerve palsy. Here, too, one sees typical associated movements; for instance, when a patient bares his teeth, he at the same time closes the eye on the affected side. The postparalytic motor phenomena seen with palsies of the third and of the seventh nerve show many other points of similarity, which will be discussed later. For the time being, suffice it to say that their associated movements seem to be of the same character.

The pathophysiology of the associated movements so commonly observed in the chronic stage of facial palsy had been much discussed in the older literature but long remained controversial. Lamy,[25] in 1905, in a short note, described the contractions following peripheral facial palsy and called them, as did Babinski,[26] *synérgiques paradoxales*. Lamy

21. Galezowski, J.: Paralysie du moteur oculaire commun avec rétraction du releveur de la paupière, Rev. neurol. **19**:544, 1910.

22. Bielschowsky, A.: Stellungsanomalien und Beweglichkeitsstörungen der Augen, Leipzig, Georg Thieme, 1922, p. 37.

23. Wilbrand, H., and Behr, C.: Die Neurologie des Auges in ihrem heutigen Stande, zugleich ein Ergänzungsband zur Neurologie des Auges von Wilbrand und Sänger, Munich, J. F. Bergmann, 1927, pt. 1, p. 32.

24. Spiegel, E. A., and Sommer, I.: Ophthalmo- und Oto-Neurologie, Berlin, Julius Springer, 1931, p. 154.

25. Lamy, H.: Note sur les contractions "synérgiques paradoxales" observées à la suite de la paralysie faciale périphérique, Nouv. iconog. de la Salpêtrière **18**: 424, 1905.

26. Babinski, J.: Hémispasme facial périphérique, Nouv. iconog. de la Salpêtrière **18**:419, 1905.

attributed them to a misdirection of regenerating fibers, to a *restauration vicieuse*. He compared these postparalytic movements of the facial muscles to movements occurring after surgical anastomosis of the accessory and the facial nerve. This note of Lamy's remained unnoticed until Lipschitz,[27] in 1906, in a monographic discussion of the subject, advanced the same hypothesis. He, too, assumed a misdirection of regenerating fibers, which grow indiscriminately from the central part of the injured nerve into the peripheral part, crossing and recrossing each other's pathways, mutually intruding into each other's channels. This hypothesis was quickly accepted everywhere. In the United States, Waterman,[28] in 1908, and Spiller,[29] in 1919, confirmed Lipschitz's view. On the basis of this theory, Spiller tried to explain not only the associated movements but the contractures which occur in cases of partial recovery from facial paralysis. The great authority of Spiller contributed much toward the popularity of Lipschitz's hypothesis. It derived strong support from the studies of Ramón y Cajal[30] and Boeke.[31] The former, in his classic work, said with regard to the restoration of the innervation in sectioned nerves:

> . . . the great majority, if not all, of the sheaths, instead of receiving the outgrowth of some axon which was present in them before the operation, are invaded by sprouts that have come from axons in other regions of the central stump.

Boeke showed that regenerating fibers grow out distorted and without pattern and frequently branch at random. Foerster[32] found that "much, undoubtedly, speaks in favor of the explanation of Lipschitz." To Cohn,[33] the great authority on peripheral nerves, this explanation seemed to be more correct than the older ones. In recent years this subject has again been taken up by several authors. They show a remarkable unanimity in their agreement with Lipschitz's view (Walsh and Craig[34];

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27. Lipschitz, R.: Beiträge zur Lehre von der Facialislähmung nebst Bemerkungen zur Frage der Nervenregeneration, Monatschr. f. Psychiat. u. Neurol. (supp.) **20**:84, 1906.

28. Waterman, G. A.: Facial Paralysis: A Study of Three Hundred and Thirty-Five Cases, Tr. Am. Neurol. A. **34**:63, 1908.

29. Spiller, W. G.: Contracture Occurring in Partial Recovery from Paralysis of the Facial Nerve and Other Nerves, Arch. Neurol. & Psychiat. **1**:564 (May) 1919.

30. Ramón y Cajal, S.: Degeneration and Regeneration of the Nervous System, translated and edited by R. M. May, London, Oxford University Press, 1928, vol. 1, p. 276.

31. Boeke, J.: De- und Regeneration des peripheren Nervensystems, Deutsche Ztschr. f. Nervenh. **115**:160, 1930.

32. Foerster, O., in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1937, vol. 3, p. 600.

33. Cohn, T., in Kraus, F., and Brugsch, T.: Spezielle Pathologie und Therapie, Berlin, Urban & Schwarzenberg, 1924, vol. 10, pt. 1, p. 224.

Ehni [35]; Coleman [36]; Martin [37]; Lyle [38]; Howe, Tower and Duel [39]). It is remarkable that this hypothesis is the only one on this subject cited in leading textbooks and handbooks (Oppenheim,[40] Sahli,[41] Wexberg,[42] Monrad-Krohn,[43] Bing and Haymaker [44]).

I myself accepted unreservedly Lipschitz's hypothesis, which has a tremendous appeal through its simplicity, as something self evident and indisputable. The positiveness of the statements of the adherents of this hypothesis and its nearly universal acceptance were most impressive. It seemed to explain not only associated movements but all other pathologic phenomena occurring after incomplete recovery from facial palsy as well.

Nevertheless, scattered remarks are found in the literature which cast doubt on the omnivalidity of this hypothesis. Holmes,[45] in 1928, expressed the belief that the cause of secondary contractures and of spontaneous twitchings of the facial muscles "is not definitely determined." Kramer [4] stated in 1936 that the interpretation of the contractures and associated movements after facial palsy still remains confused and that a satisfactory explanation of this phenomenon is still lacking. The reviews given on this subject by Petz,[46] in 1933, and by Nussbaum,[47] in 1936, are confusing and inconclusive. The latter stated:

> The great number of the theories and hypotheses reviewed here shows that it is difficult even today to gain a clearcut and all-embracing picture of the genesis and physiopathology of the late symptoms of peripheral facial palsy.

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34. Walsh, M. N., and Craig, W. M.: Posttraumatic Faulty Regeneration of the Vagus Nerve and Branches of the Cervical Plexus, Proc. Staff Meet., Mayo Clin. **15**:117, 1940.

35. Ehni, G.: Facial Twitching, Proc. Staff Meet., Mayo Clin. **19**:129, 1944.

36. Coleman, C. C.: Surgical Lesions of the Facial Nerve with Comments on Its Anatomy, Ann. Surg. **119**:641, 1944.

37. Martin, R. C.: Repair of Peripheral Injuries of the Facial Nerve, J. Nerv. & Ment. Dis. **99**:755, 1944.

38. Lyle, D. J.: Neuro-Ophthalmology, Springfield, Ill., Charles C Thomas, Publisher, 1945, p. 92.

39. Howe, H. A.; Tower, S. S., and Duel, A. B.: Facial Tic in Relation to Injury of the Facial Nerve, Arch. Neurol. & Psychiat. **38**:1190 (Dec.) 1937.

40. Oppenheim,[5] p. 766.

41. Sahli, H.: Lehrbuch der klinischen Untersuchungsmethoden, ed. 6, Leipzig, Franz Deuticke, 1920, vol. 2, p. 935.

42. Wexberg, E., in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1936, vol. 9, p. 118.

43. Monrad-Krohn, G. H.: Clinical Examination of the Nervous System, ed. 7, New York, Paul B. Hoeber, Inc., 1938, p. 51.

44. Bing, R., and Haymaker, W.: Textbook of Nervous Diseases, St. Louis, C. V. Mosby Company, 1939, p. 82.

45. Holmes, G., in Osler, W.: Modern Medicine, ed. 3, London, Henry Kimpton, 1928, vol. 6, p. 420.

(Footnotes continued on next page)

HYPOTHESIS OF MISDIRECTED FIBERS FOR THE EXPLANATION OF ASSOCIATED MOVEMENTS IN OCULOMOTOR MUSCLES

The famous ophthalmologist Bielschowsky,[48] who died in 1940, and who in his time was the greatest authority on the motility of the eye, applied in numerous publications, the first appearing in 1910, the hypothesis of Lipschitz to explain associated movements after oculomotor palsy. The leading French neurologist Thomas [49] stated in 1910, independently of Bielschowsky, that the associated movements of the oculomotor muscles after third nerve palsy could be explained in the same way as associated movements after facial nerve palsy—*par une régénération défectueuse des fibres nerveuses.* Authors of various countries accepted readily the hypothesis of Lipschitz and Bielschowsky—Tamamscheff [50] (Russia), Coppez [8] (Belgium) and Abramowicz [51] (Poland), to name only a few. In 1935 Bielschowsky [52] explained the pseudo-Graefe sign as follows:

> Suppose that the continuity of the third nerve is interrupted by a trauma or a tumor. In the course of healing, some of the nerve fibers which proceed from the central part of the trunk of the third nerve do not find their original sheaths in the peripheral part of the nerve but go astray, so that they arrive at muscles to which they do not belong. For instance, the fibers from the nucleus intended for the internal rectus arrive not at this muscle but at the levator of the upper lid, so that the impulse for adduction produces lifting of the upper lid, even if it cannot be lifted by a direct innervation effort because the fibers coming from the levator nucleus have gone astray.

In a review of this subject, Bielschowsky [53] stated in 1936 that the explanation given by Lipschitz for associated movements in the course

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46. Petz, M.: Ueber Kontrakturen und Mitbewegungen nach alter peripherer Facialislähmung, Arch. f. Psychiat. **100**:379, 1933.

47. Nussbaum, M.: Ueber die Physiopathologie der Spätsymptome nach Lähmungen im Gebiet des peripheren Teils des Nervus facialis, Inaug. Dissert., Basel, 1936.

48. Bielschowsky, A. (*a*) Mitbewegungsphänomene bei Augenmuskellähmungen, Berl. klin. Wchnschr. **27**:367, 1910; (*b*) Die Bedeutung der Bewegungsstörungen der Augen für die Lokalisierung zerebraler Krankheitsherde, Ergebn. d. Chir. u. Orthop. **9**:123, 1916; (*c*) Die Motilitätsstörungen der Augen, in Graefe, A., and Saemisch, T.: Handbuch der gesamten Augenheilkunde, ed. 2, Berlin, Julius Springer, 1910, vol. 8, pt. 2, chap. 11, p. 395.

49. Thomas, A., in discussion on Galezowski.[21]

50. Tamamscheff, C.: Paradoxe Bewegungen des oberen Lides bei der Okulomotoriuslähmung (Pseudo-Graefesches Phänomen), Klin. Monatsbl. f. Augenh. **48**:479, 1910.

51. Abramowicz, I.: On the Clinical Features of Oculomotor Paralysis, Klin. oczna **11**:444, 1933; abstracted, Zentralbl. f. d. ges. Neurol. u. Psychiat. **72**:244, 1934.

52. Bielschowsky, A.: Lectures on Motor Anomalies of the Eyes, Arch. Ophth. **13**:33 (Jan.) 1935.

of facial palsy is the most plausible and the most natural one for the motor phenomena occurring after oculomotor nerve palsy. In their monumental handbook on the neurology of the eye, Wilbrand and Behr,[54] leading German ophthalmologists, stated explicitly that they agree with the explanation of the pseudo-Graefe phenomenon as given by Bielschowsky,[48] which is based on the theory of Lipschitz.

Extensive research has been done in recent years on the problem of associated movements in the muscles innervated by the oculomotor nerve. Researchers and reviewers agree that these associated movements are due to "faulty peripheral nerve regeneration" (Bender[55]; Bender and Alpert[56]; Bender and Fulton[57]; Ford and Woodhall[58]; Ford, Walsh and King[59]; Walsh and King[60]; Walsh[61]; Spiegel and Sommer[62]; Dandy[63]). In his monumental work on ocular neurology, the only one of its kind in Spanish, Adrogué[64] accepted Bielschowsky's theory of the pseudo-Graefe phenomenon and cited the experimental work of Bender and Fulton as a confirmation of that theory. In a book published in 1944, Ford[65] stated that the abnormal motor phenomena associ-

53. Bielschowsky, A.: Symptomatologie der Störungen im Augenbewegungsapparat, in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1936, vol. 4, p. 205.

54. Wilbrand and Behr,[28] p. 38.

55. Bender, M.: The Nerve Supply to the Orbicularis Muscle and the Physiology of Movements of the Upper Eyelid, Arch. Ophth. **15**:21 (Jan.) 1936.

56. Bender, M. B., and Alpert, S.: Abnormal Ocular and Pupillary Movements Following Oculomotor Paralysis, Arch. Ophth. **18**:411 (Sept.) 1937.

57. Bender, M. B., and Fulton, J. F.: Functional Recovery in Ocular Muscles of a Chimpanzee After Section of Oculomotor Nerve, J. Neurophysiol. **1**:144, 1938; Factors in Functional Recovery Following Section of the Oculomotor Nerve in Monkeys, J. Neurol. & Psychiat. **2**:285, 1939.

58. Ford, F., and Woodhall, B.: Phenomena Due to Misdirection of Regenerating Fibers of Cranial, Spinal and Autonomic Nerves, Arch. Surg. **36**:480 (March) 1938.

59. Ford, F. R.; Walsh, F. B., and King, A. B.: Clinical Observations on the Pupillary Phenomena, Bull. Johns Hopkins Hosp. **68**:309, 1941.

60. Walsh, F. B., and King, A. B.: Ocular Signs of Intracranial Saccular Aneurysms, Arch. Ophth. **27**:1 (Jan.) 1942.

61. Walsh, F. B.: Certain Abnormalities of Ocular Movements: Their Importance in General and Neurologic Diagnosis, Bull. New York Acad. Med. **19**:253, 1943.

62. Spiegel, E. A., and Sommer, I.: Neurology of the Eye, Ear, Nose and Throat, New York, Grune & Stratton, Inc., 1944, pp. 202 and 375.

63. Dandy, W. E.: Intracranial Arterial Aneurysms, Ithaca, N. Y., Comstock Publishing Company, Inc., 1944, p. 11.

64. Adrogué, E.: Neurología ocular, Buenos Aires, El Ateneo, 1942, p. 128.

65. Ford, F. R.: Diseases of the Nervous System in Infancy, Childhood and Adolescence, ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1944, pp. 69 and 70.

ated with regenerated third and seventh nerves are "due to the misdirection of regenerating nerve fibers." Walsh [61] stated that it has been proved to be so.

CRITIQUE OF THE HYPOTHESIS OF MISDIRECTION OF REGENERATING NERVE FIBERS

Despite these positive statements from authoritative neurologic, ophthalmologic and physiologic sources, the problem seems as yet unsolved. To the hypothesis of misdirection of regenerating fibers, so widely accepted, the following objections must be brought forth:

1. When one approaches the problem from a purely clinicophysiologic standpoint, it seems that such a lawless sprouting out of regenerating fibers, deviating from their course, must be considered the exception, not the rule. It can hardly be assumed that all fibers go astray. Of course it is not known how many misdirected fibers are necessary or sufficient to produce associated movements, but the universality of associated movements in a given case would imply a misdirection of all the fibers. Even if and when a misdirection of regenerating fibers takes place, there is no proof that this misdirection is the cause of the ensuing manifold, widespread and intensive associated movements. The direct deduction that anatomic changes produce such a physiologic effect cannot, and should not, be blindly accepted as the basis for discussion. Also, if the regenerating fibers have the alleged strong and universal tendency toward misdirection which accounts for postparalytic associated movements, such movements should, then, always occur in every case of injury to the third or the seventh nerve; this is not the case. Associated movements occur often after injury to the third or the seventh nerve, but by no means always.

2. It would be understandable if misdirection of regenerating fibers were to occur only in cases of traumatic or surgical palsy, especially in cases in which nerves are sutured. Here the nerve undergoes some displacement. But one usually finds associated movements also in cases of simple "rheumatic" facial palsy and of infections of the third nerve, in which no mechanical trauma to the nerve could have taken place. Associated movements appear, for instance, after facial neuritis in the fallopian canal, where the nerve is well protected against spatial changes. Conspicuous associated movements occur in cases in which the nerve was not severed, in which the relationship of the central and the peripheral end of the nerve was not disturbed. Here, regeneration in the old established paths could easily have taken place. It is incomprehensible why such a misdirection, leading to intensive and extensive associated movements, should occur here at all.

3. If misdirection of regenerating fibers of any import does take place on recovery of the nerve, it would be natural to assume that this

misdirection would be more intensive and extensive in surgical cases than in cases of primary neuritis or perineuritis. Special investigations on this point are lacking. From a review of the cases in the literature, however, together with the cases presented here, no support can be found for the assumption that traumatic or surgical palsies of the third or seventh nerve are more likely to be followed by associated movements than are purely neuritic ones. I have often seen very marked associated movements after mild "rheumatic" facial palsy. In cases of traumatic palsy there does not seem to be a greater tendency toward associated movements. The following statement of Martin,[37] who has had wide experience along these lines, is remarkable in this connection:

> Patients who have recovered from a Bell's palsy frequently have the corner of the mouth twitch when reflex winking occurs. Post-traumatic cases do not show this often.

This observation speaks positively against the hypothesis of misdirection, since according to it just the opposite should be expected—in the cases of post-traumatic palsy associated movements should occur more frequently.

4. Postparalytic associated movements usually do not occur after infectious or traumatic lesions of nerves other than the third and the seventh. Such a case has never come to my attention, either during or after World War I. If associated movements were to occur in cases of palsy of spinal peripheral nerves after trauma, neuritis or operation, as they do in cases of third or seventh nerve palsy, the prognosis in such cases would indeed be quite different than it actually is. Suppose these associated mass movements were to occur in cases of radial palsy. The patient would move simultaneously all the radial muscles on innervating a single one! In such a case a limb would hardly be of practical use. The mass movements would be almost unendurable, and surgical treatment of peripheral nerves would be almost nonexistent. Occasionally associated movements have been seen with lesions of peripheral nerves. But this has been reported only after use of sutures (Foerster,[32] Ford and Woodhall [58]), and even then these phenomena are rare.

5. When an irregular sprouting of the fibers growing from the central into the peripheral end of a locally damaged nerve does occur, it is quite natural to assume that fibers from neighboring compartments would intermingle more readily. If there are, e. g., five parallel compartments, then compartments 1 and 2, 2 and 3, etc., would show more intermingling, and thus more mutual associated movements, than, for instance, compartments 1 and 5. A great amount of work has been done on morphologic segmentation and functional localization of the components of the oculomotor nucleus. Reference may be made here

to the work of Brouwer.[66] Riley[67] wrote an excellent review on this subject. The latest investigation is that of Bender and Weinstein,[68] who concluded:

> The functional representation of the ocular muscles in the oculomotor nucleus is as follows in dorso-ventral and rostro-caudal directions (1) sphincter pupillae (usually bilateral responses), (2) inferior rectus, (3) inferior oblique (?), (4) internal rectus, (5) superior rectus, and (6) levator palpebrarum. The functional arrangement in the oculomotor roots is the same as in the nucleus.

The textbooks accepted this scheme of the topography of the oculomotor nucleus, which is practically the same as that of Bernheimer,[69] published in 1897. On careful analysis of the associated movements in my cases, one would have to conclude (*a*) that fibers from neighboring compartments usually do not intermingle, (*b*) that fibers from remote compartments do intermingle most and (*c*) that the associated movements among them constitute the leading symptom in the postparalytic associated movements. The nucleus and the fibers of the rectus superior lie next to those of the levator palpebrae. One would expect that the fibers of these two muscles would intermingle most freely. This, however, is not the case, and there are no associated movements from the levator palpebrae. There are, to be true, associated movements from the rectus superior to the levator, but these are by no means prominent. Fuchs[6] listed the elevation of the lid on looking upward as a "rare complication." Bielschowsky[48a] reported a case in which there were marked associated movements in the muscles supplied by the third nerve but no elevation of the lid on looking up. The most important associated movements occur between the rectus internus and the levator palpebrae—and the nerve fibers of these two muscles are widely separated in their course! The pseudo-Graefe sign, which is so prominent in these associated movements, is due to a connection between the fibers to the rectus inferior and those to the levator palpebrae. The compartments for these two muscles lie at the two ends of the elongated oculomotor nucleus and are separated by the compartments of the rectus superior, the rectus internus and the obliquus inferior! To explain the pseudo-Graefe sign through misdirection of fibers, it must be assumed that the fibers from the rectus inferior have passed nearly all other fibers of the oculomotor nerve in order to reach the

66. Brouwer, B.: Klinisch-anatomische Untersuchung über den Oculomotoriuskern, Ztschr. f. d. ges. Neurol. u. Psychiat. **40**:152, 1918.

67. Riley, H. A.: The Central Nervous System Control of the Ocular Movements and Disturbances of This Mechanism, Arch. Ophth. **4**:640 (Nov.) 1930.

68. Bender, M. B., and Weinstein, E. A.: The Functional Pattern Within the Oculomotor Nucleus, Tr. Am. Neurol. A. **68**:48, 1942.

69. Bernheimer, S.: Experimentelle Studien zur Kenntniss der Innervation der inneren und äusseren von Oculomotorius versorgten Muskeln des Auges, Arch. f. Ophth. **44**:481, 1897.

levator muscles, which are the most remote. There can hardly be any explanation for such an elaborate misdirection.

6. The cardinal feature in postparalytic associated movements of the third nerve is the ease with which the levator palpebrae reacts to impulses sent to other muscles. This occurs also in cases in which the levator palpebrae is completely paralyzed. Sattler,[70] explaining the pseudo-Graefe symptom, stated that here an impulse of innervation irradiates into pathways which are less damaged. This is not quite correct, since the pathways—for instance, those for the levator palpebrae—may be completely blocked for voluntary innervation and still the pseudo-Graefe phenomenon may occur. There is no doubt that the levator palpebrae may move on innervation of the rectus inferior or the rectus internus and otherwise be completely paralyzed. Bielschowsky [22] reported such a case. Here the paralyzed upper lid could not be lifted in the slightest, not even with the strongest effort. The complete paralysis of the levator palpebrae means that none of the fibers from its nucleus has reached the muscle. They must be totally misdirected to other muscles. But where to? There is no evidence for such misdirection, since there are in cases of paralysis of the levator no associated movements in any other oculomotor muscle—not even in traces—when the levator is innervated. It must, then, be assumed that all the fibers leading to the levator palpebrae have reached nowhere—that they have been blocked completely, a condition which is difficult to conceive. This is all the more difficult when it is recalled that there are cases in which, in the presence of associated movements in the oculomotor muscles, there is complete paralysis of the levator palpebrae and of the rectus superior muscle—and no associated movement from these to other muscles! Adherents of the Lipschitz-Bielschowsky hypothesis owe an explanation as to how it is possible that some fibers get completely lost and why this happens predominantly to nerve fibers destined for the levator palpebrae.

7. Associated movements in oculomotor muscles, with their cardinal symptom of automatic elevation of the lid on looking inward and downward, do occur in cases in which the levator palpebrae has recovered completely. The literature is replete with such interesting reports. Bielschowsky [52] described such a case in detail. According to the text and judging from the illustrations, the levator palpebrae was completely normal. On another occasion he spoke of a pseudo-Graefe phenomenon occurring when the ptosis had almost, or completely, disappeared.[48b]

70. Sattler, H.: Basedow'sche Krankheit, in Graefe, A., and Saemisch, T.: Handbuch der gesamten Augenheilkunde, Leipzig, Wilhelm Engelmann, 1908, vol. 9, pt. 2, chap. 14, p. 79.

Sinclair,[71] in classifying the numerous types of abnormal associated movements of the lids, listed group 4, in which there is no ptosis. Hinkel[72] reported that in his case the ptosis disappeared. Bender[55] based his first study of postparalytic movements of the third nerve on a case in which there was no ptosis. Fuchs[6] stated ". . . . it can happen that the ptosis disappears and yet the pseudo-Graefe continues." If the levator palpebrae in the course of regeneration of the nerve after palsy has been restored to normal, it can mean only that all the fibers which belong to the levator palpebrae have reached their destination. Its compartment is filled. The *status quo ante* has been restored. But in such a case associated movements may still be present spreading, say, from the rectus internus to the levator palpebrae. How could this be possible if the levator palpebrae has become normal? Its complete restoration can mean only that the whole of its compartment has been filled, and with its own fibers, which are now in their respective places. How, then, could, and why should, fibers of the rectus internus "squeeze" into the already completely filled compartment; and if some fibers of the rectus internus did penetrate the compartment of the levator, and fill it, together with the first arrived levator fibers, how, then, is it possible that the other levator fibers could "squeeze" into this already filled compartment? The compartment of the levator must have been filled with its own fibers, since the muscle does not show the slightest sign of paresis. A mass immigration into the compartment of the levator of the fibers innervating the rectus internus muscle would have to take place to explain the strong associated movement. A few misdirected fibers could hardly account for such a powerful contraction of the levator palpebrae on innervation of the rectus internus. In order to explain the phenomena of associated movements involving the levator muscle in the absence of ptosis, it must be assumed that one compartment can be filled beyond normal capacity at the expense of some other compartment. This is difficult to conceive.

8. The regenerating fibers growing from the point of lesion toward the periphery need time to reach their own, or other, muscles, It is generally assumed that the axons grow at the rate of 1 mm. a day. If associated movements are due to misdirection, they should appear earlier with more distally located lesions of the third or the seventh nerve than with the more proximally located lesions. From a cursory survey this does not seem to be the case. Exact investigations on this subject, however, are lacking. Case 2 raises another question. Here, after a lesion of the oculomotor nerve which followed trauma to the skull,

71. Sinclair, W. W.: Abnormal Associated Movements of the Eyelids, Ophth. Rev. **14**:307, 1895.

72. Hinkel: Das Pseudo-Graefe'sche Symptom in Anschluss an Augenmuskellähmungen, Inaug. Dissert., Rostock, 1902.

associated movements were noted thirty-five days after the injury. How much earlier they might have appeared cannot be stated. Dr. J. B. de C. M. Saunders (personal communication) estimates the length of the oculomotor nerve from its emergence at the base of the brain to its insertion into the muscles as being 5 to 5.5 cm. If the lesion occurred in the most proximal part of the nerve—which is most likely—the time interval would have been too short for the nerve to traverse this distance, especially if the growth of its fibers was complicated by aberration. I have seen associated movements appear so early after infectious neuritis of the seventh nerve that the growing out of the damaged fibers into the muscles could hardly have taken place in so short a time. The time element deserves special consideration in future discussions of this problem.

9. It is difficult to establish clinically the diagnosis of a peripheral versus a nuclear third nerve palsy. It is, however, a well known fact that nuclear palsies of the cranial nerves in general, and those of the third nerve in particular, do occur after injury to the skull. From Tietze's [73] review of the literature one learns of the certain existence of such nuclear post-traumatic third nerve palsies. Spiller [74] showed an isolated nuclear third nerve palsy histologically. This was due to thrombotic closure of the small arteries supplying the nuclei of the oculomotor nerve. As to the probable central origin of oculomotor nerve palsy which later leads to associated movements of the oculomotor muscles, it is interesting to note that Gowers,[10] who first described a case of this condition, assumed that the lesion was "probably central." Köppen,[11] in a histologic study of his case, found striking vascular changes in the area of the nucleus of the third nerve. Fuchs [7] assumed that a primary lesion of the nucleus existed in 2 of his cases, as did Galezowski.[21] Wilbrand and Behr [23] even stated that "the pseudo-Graefe phenomenon can occur with both peripheral and—as is more often the case—with central lesions." As to the associated movements occurring after nuclear lesions of the seventh nerve, there are so many pertinent and well substantiated reports that it is hardly necessary to cite any of them here. From what is known on this subject, it must be assumed that such movements do occur when the lesion is located in the nucleus of the seventh nerve itself. Such a lesion to the nucleus or to its efferent system is, of course, not complete, either quantitatively or qualitatively; some elements capable of regeneration must remain

73. Tietze, A., in von Bruns, P.: Neue deutsche Chirurgie, Stuttgart, F. Enke, 1916, vol. 18, pt. 2, p. 129.

74. Spiller, W. G.: Bilateral Oculomotorius Palsy from Softening in Each Oculomotorius Nucleus, Névraxe **14**:125, 1913.

intact, or otherwise no regeneration and no restoration of movement of any kind could take place. When postparalytic associated movements occur—as they certainly do—with nuclear lesions of the third or the seventh nerve, it is diffcult to comprehend, first, how such a misdirection could take place at all, especially with inflammatory or degenerative disease, and, second, how it could produce exactly the same results as does a peripheral injury to the nerve itself. It would be quite natural to assume that if the nucleus was damaged no misdirection could occur and the fibers might have the opportunity to leave the nucleus in their preformed channels. The whole theory of misdirection evidently is applicable only to the cases of lesions of the nerve trunk, and not to cases of nuclear lesions.

10. The hypothesis of misdirection of regenerating fibers has one absolute prerequisite, a *conditio sine qua non,* so to say: The lesion must lie on the trunk of the third or the seventh nerve before it branches off to the various muscles which participate in the mutual associated movements. But it is a fact that associated movements do occur after damage to a single peripheral branch of the third or the seventh nerve, and this at some distance from the point where it leaves the main trunk. Bittorf [75] described such cases involving the seventh nerve. He saw, for instance, associated movements consisting of wrinkling of the skin of the chin on closing the eye in a case of an old, mild injury to the distal part of the ramus mentalis. Furthermore, he saw associated movements extending to the platysma muscle in cases of isolated injury of the facial branch to the mouth. Kramer [4] stated:

> . . . After injury to single branches of the facial nerve, for instance, after lesions incurred in duels or with bullet wounds of the cheek, which is followed by isolated paresis of the muscles of the upper lip, associated movements occur. It is remarkable that in cases of such injury the innervation of the orbicularis oculi muscle, which had not been damaged, brings about an associated movement of the upper lip.

I have observed such cases, which were described by a pupil of mine (Petz [46]). Since this report other similar observations have left no doubt in my mind that associated movements do occur on injury of a peripheral branch of the facial nerve, movements involving muscles innervated by branches of the nerve which have not been injured in any way.

With respect to the third nerve, similar observations are on record. Hinkel [72] saw associated movements in the oculomotor muscles when the lesion to the oculomotor nerve had occurred in the orbit. In this connection, a remarkable case was described by Halpern,[76] but all too briefly. A young man shot himself in the right temple in an attempt at

75. Bittorf, A.: Ueber Mitbewegungen im Facialisgebiet, Deutsche Ztschr. f. Nervenh. **121**:221, 1931.

76. Halpern, L.: On the Pseudograefic Symptom, Harefuah **8**:111, 1934.

suicide. The bullet remained at the base of the brain on the right side. The right eye showed isolated complete ptosis. After three months the patient displayed the pseudo-Graefe symptom: He was unable to lift the ptotic lid, but it moved involuntarily when he looked downward. Here there was an associated movement in the levator palpebrae on innervation of the rectus inferior muscle, and this in a case in which only the branch of the oculomotor nerve leading to the levator palpebrae muscle was injured.

In those cases in which associated movements appear in facial or oculomotor muscles when only a terminal branch of the nerve to these muscles has been damaged, the theory of misdirection must fail completely. According to this hypothesis, one would have to assume here a retrograde regeneration of the affected terminal branch to the main track of the nerve and forward regeneration along unaffected branches—an impossible assumption!

11. Associated movements, though of mild degree, may occur both in muscles supplied by the seventh nerve and in muscles supplied by the third nerve in cases in which no injury and no palsy has ever taken place. These movements, thus, can occur in otherwise completely normal nerves. Kramer [4] stated: "In rare cases the same associated movements can be seen without a facial palsy having previously occurred." I have seen many a case of associated movements in the facial muscles in completely normal intelligent persons who had never been aware of this anomaly. I observed it also in cases of extrapyramidal diseases and in 1 case of amyotrophic lateral sclerosis. There are certain persons who show, so to speak, some kind of motor infantilism in their facial muscles, consisting in lack of differentiation, i. e., a tendency to perform mass movements instead of single ones. In the area of the third nerve, too, associated movements were noticed when no paralysis of the ocular muscles was or ever had been present. So many definite cases of this kind are reported in the literature that there can be no room for doubt. Here a misdirection of regenerating fibers cannot be incriminated in any way.

12. Associated movements in oculomotor muscles can exist as a congenital anomaly. One of the first cases described, that of Browning,[9] belongs to this group. Fuchs [7] compared this condition with the syndrome of Marcus Gunn which in most cases represents a congenital anomaly. Friedenwald,[77] compiling cases of associated movements of the eyelids, found 12 in which the condition was congenital. Of recently described cases of the congenital pseudo-Graefe phenomenon that of

77. Friedenwald, H.: On Movements of the Eyelids Associated with Movements of the Jaws and with Lateral Movements of the Eyeballs, Bull. Johns Hopkins Hosp. **7**:134, 1896.

Volmer [78] may be mentioned. Here this abnormality could be seen in 6 members of a family, covering four generations on the paternal side. In some cases of the congenital type there is absence of any other pathologic sign, such as ptosis; there are associated movements only. In cases in which the condition is congenital, and no injury to the nerve has ever taken place, the theory of misdirection of regenerating fibers, of course, fails completely to give a satisfactory physiologic explanation.

13. There is a rare condition—congenital or acquired—called cyclic or rhythmic oculomotor nerve paralysis. This is characterized by alternating automatic phases of spasm and relaxation affecting various branches of the more or less paralyzed oculomotor nerve. Selinger [79] reported the appearance of the pseudo-Graefe sign in the spastic stage in such a case. Hicks and Hosford [80] observed the same phenomenon during both the spastic and the relaxed phase. Here misdirection of fibers could not have taken place and could not be blamed for the associated movements.

14. It is worth while to note that associated movements—of the same type as those which occur after incomplete recovery from facial palsy—do occur in facial muscles which have never been paralyzed but which have been the site of another hyperkinesis, the so-called hemifacial spasm. Here, both the associated movements and the spasm urgently require a common explanation, which the hypothesis of misdirection does not and cannot offer. The following is an illustrative case:

A 55 year old man had suffered for three years from tonic-clonic spasms of the muscles of the right side of the face. There were no objective signs otherwise. The muscles of the right side of the face were normal in the intervals between spasm. There was no indication of any source of irritation. A psychogenic origin could be excluded by the fact that some of the tonic-clonic spasmodic movements of the muscles were such that they could hardly be imitated voluntarily. Figure 5 *a* shows the patient at rest. Hardly any abnormality can be seen. Figure 5 *b* shows associated movements in the muscles of the corner of the mouth on closing of the eyes. These associated movements occurred only on firm closing, and not on light closing. Figure 5 *c* shows associated movements in the orbicularis oculi on baring of the teeth. These associated movements occurred only in the facial muscles. There were no associated movements in any of the facial muscles when the muscles

78. Volmer, W.: Erbliche, abnorme Mitbewegung des Oberlides, Klin. Monatsbl. f. Augenh. **73**:135, 1924.

79. Selinger, E.: Cyclic or Rhythmic Oculomotor Paralysis, Arch. Ophth. **4**:32 (July) 1930.

80. Hicks, A. M., and Hosford, G. N.: Cyclic Paralysis of the Oculomotor Nerve, Arch. Ophth. **17**:213 (Feb.) 1937.

of the trigeminal nerve, for instance, were innervated, e.g., when the patient squeezed a tongue blade tightly between his teeth. All the photographs were taken while the patient was completely at rest. The associated movements shown here, produced in other facial muscles when only part of them is innervated, cannot be regarded as a spasmodic contraction provoked by the voluntary movements. This is true for the following two reasons: (1) the associated movements produced here artificially ceased at once when the voluntary movement stopped; (2) these associated movements were not accompanied, as in a spontaneous spasm, with hyperkinesis in such forms as fine twitchings and fibrillations.

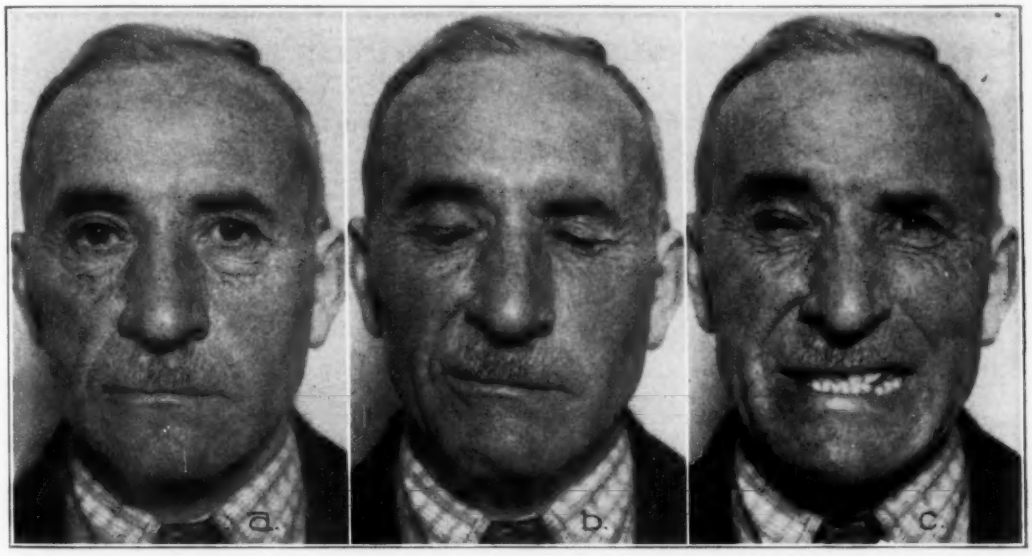

Fig. 5 (case 5).—Associated movements in the facial muscles in a case of right-sided cryptogenic hemifacial spasm. The patient is shown (*a*) at rest, (*b*) with his eyes closed and (*c*) showing his teeth.

Since I have found associated movements in cases of cryptogenic hemifacial spasm, former patients with this condition have been reexamined for associated movements, and every new patient has been checked for this condition. Associated movements have been found present in every case and were mostly unnoticed by the patients even when the condition had persisted for many years.[80a]

This constant association of cryptogenic hemifacial spasm with associated movements in the affected muscles is a remarkable phenomenon which is of import to the present discussion. Here, there are associ-

80a. Pitres, A., and Abadie, J.: Hémispasmes syncinétiques de la face, Nouv. iconog. de la Salpêtrière **26**:363, 1913.

ated movements of the facial muscles exactly as they are seen after paralysis, but certainly no misdirection of any fibers could account for their existence.

15. If the misdirection of regenerating fibers were to produce associated movements, it would be quite justifiable to assume that—since such a misdirection is completely anarchistic, lawless, and cannot have any established pattern—the ensuing associated movements should be of a great variety. The movements should vary in different persons and should range, so to speak, from 1 to 100 per cent in their variations and modifications. This is not the case. There is a definite pattern for the associated movements of the seventh nerve: each muscle of the seventh nerve contracts simultaneously on voluntary innervation of any other facial muscle. This is, of course, most conspicuous in the mutual reactions of the orbicularis oculi muscle and the muscles innervating the corner of the mouth. But less prominent muscles, such as the platysma, participate also in the associated movements. All the facial muscles act here as a unit. These muscles contract not only on voluntary innervation of a single muscle but on reflexive contraction of any of them. Many a reflex described in the regenerating facial muscles is nothing else than an associated movement. Mondino [81] described in 1907 a "special reflex observed with facial contracture: In cases of facial contracture occurring in association with peripheral nerve palsy, tapping the supraorbital nerve at the point of its emergence produces a reflexive contraction in the muscles of the lower branch of the facial nerve." Referring to Mondino, Purves-Stewart [82] stated: "The spastic facial muscles can also be made to contract reflexly by tapping lightly over the point of emergence of the most accessible branch of the fifth, viz., the supraorbital nerve." Buzzard [83] reported the same phenomenon: "A tap on the supra-orbital branch of the fifth nerve often produces a contraction of the muscles at the corner of the mouth in this condition." As was pointed out elsewhere (Wartenberg [84]), this tapping elicits the orbicularis oculi reflex, consisting of a contraction of this muscle. This reflex has, of course, no connection with the supraorbital nerve, since tapping the glabella or any other point around the muscle can elicit it. This reflexive contraction of the orbicularis oculi muscle produces, in turn, an associated contraction in the muscles innervated by the lower branch of the facial

81. Mondino, C.: Di uno speciale riflesso che si osserva nella contrattura facciale, Riv. di pat. nerv. **12**:49, 1907.

82. Purves-Stewart,[15] p. 269.

83. Buzzard, E. F.: Varieties of Facial Spasm and Their Treatment, Practitioner **91**:745, 1913.

84. Wartenberg, R.: Studies in Reflexes, Arch. Neurol. & Psychiat. **51**:113 (Feb.) 1944.

nerve. This "reflex" was rediscovered by Myerson [85] in 1920. In the description of this phenomenon, he was more correct than Mondino when he stated: "Tapping the forehead or the bridge of the nose causes a contracture (reflex) of the affected corner of the mouth." The muscles of the chin and the platysma muscle also participate in these mutual movements, both on voluntary and on reflexive stimulation of other facial muscles. I observed repeatedly that on tapping the glabella, as for the elicitation of the orbicularis oculi reflex, there was a distinct contraction of the platysma, on its medial border, under the chin. Rendu [86] stressed the fact that the superior and posterior auricularis muscles, innervated by the facial nerve, also participate in the associated movements: There is an involuntary upward movement of the auricle on contraction of the orbicularis oculi muscle. Ford and Woodhall,[58] in describing their case of "rheumatic" palsy of the seventh nerve, remarked:

> . . . On repeated tests it was evident that whenever the patient moved any part of the right side of the face every muscle supplied by the seventh nerve on that side contracted to some extent.

Coleman [87] stated:

> . . . the entire facial musculature on the affected side is made a single functional unit and with every movement the facial muscles move *en masse*.

All this serves to demonstrate the total character of the associated movements in the muscles controlled by the seventh nerve. This is due to the fact that all the facial muscles participate in these movements on a mutual basis. These movements are based on the "all for one" principle. This pattern of associated movements is constant in all cases. No muscle is excluded; no muscle, or combination of muscles seems to have any dominant priority, although, of course, the visible manifestations of these movements are more prominent in some muscles than in others. Apparently, the function and location of these muscles make their movements more discernible. Occasionally these movements are only rudimentary. This is apparently due to a severe lesion of "the final common path." Such a lesion may block the path almost completely and permit only vestigial impulses to pass. The associated movements of the facial nerve seem to prove that the underlying lesion has transformed all the facial muscles into a compact, inseparable unit, with all participants equally active. If this is due to misdirection of regenerating fibers, one must

85. Myerson, A.: Reflex Phenomena in the Contracture Stage of Peripheral Facial Paralysis, J. Nerv. & Ment. Dis. **52**:239, 1920.

86. Rendu, R.: Syncinésie palpébro-auriculaire dans la paralysie faciale, J. de méd. de Lyon **7**:417, 1926.

87. Coleman, C. C.: Results of Faciohypoglossal Anastomosis in the Treatment of Facial Paralysis, Ann. Surg. **111**:958, 1940.

assume that this misdirection occurs from all the compartments of the facial trunk and occurs with absolute regularity in every case, that the fibers from any one compartment go constantly astray to all other compartments and are equally distributed among them and that no compartment is spared. Needless to say, such an assumption is not tenable.

There is a definite pattern also for the associated movements of the muscles supplied by the third nerve, which consists of (1) ready responsiveness with which the levator palpebrae and the rectus internus muscle react to any innervation of any other muscles of the third nerve and (2) close association of movements between the rectus internus and, to a lesser degree, the rectus inferior on one side and the levator palpebrae on the other side.

In the literature one finds numerous references to the stereotyped, monotonous associated movements in the muscles of the third nerve. Sinclair's [71] classification of the abnormal associated movements of the eyelids has, in series 2, cases in which contraction of the levator palpebrae superioris automatically follows the contraction of the rectus internus. This series may be regarded as a paradigm for all pathologic associated movements of the muscles of the third nerve. These two muscles show the greatest tendency toward associated movements. Ford, Walsh and King [59] stated correctly and very pertinently: "No matter what movement is attempted, the bulb is adducted and the lid lifts." This regularity of associated movements is so striking that an attempt has been made to explain it by assuming that the regenerating fibers, in their deviation from their own course, prefer certain routes and that these particular routes are most commonly entered. Bielschowsky [22] said, for instance, that "the route to the levator palpebrae appears to be especially easily accessible." No reasonable explanation can be given why certain regenerating fibers should prefer to enter certain routes which belong to other fibers and why these routes should be so easily accessible. How is it possible to explain why the fibers which belong in the compartment of the rectus internus insist, with constant stubbornness, on going astray in one particular direction while "jaywalking," namely, into the compartment of the levator palpebrae, which is not even their neighboring compartment? Whatever may be the explanation for the pattern of the associated movements in the muscles of the seventh and third nerves, there is no doubt that such a pattern exists and that the associated movements do not display any chaos in their manifestations. A misdirection of fibers, which in itself can be only completely irregular, could not produce such well behaved associated movements. Observing them, one must say: "There is too much order in this disorder!"

The associated movements after incomplete recovery from the seventh or the third nerve palsy are thus always the same, regardless of the site and nature of the disorder, its cause and the condition of the patient. Associated movements appear in the facial muscles no matter whether the lesion is diffuse or localized or where in its course the nerve is affected. I have seen exactly the same associated movements in the facial muscles after a local injury and after recovery from Guillain-Barré-Strohl polyneuritis. As far back as 1872, Hitzig [88] mentioned that the associated movements seem to be completely independent of the site and the nature of the lesion. The same view was held by Lipschitz,[27] according to whom only the severity of the lesion is important. The same applies to the third nerve. Von Michel,[89] in 1908, stressed that the site and the causes of the third nerve palsy seem to be irrelevant to the appearance of associated movements. Coppez [8] and Camison [90] emphasized this recently. The same associated movements in the oculomotor muscles have been observed after such diversified morbid conditions affecting the third nerve as pressure from a saccular aneurysm of the internal carotid artery, polioencephalitis superior acuta, trauma to the skull, syphilis-tabes-dementia paralytica, postdiphtheritic polyneuritis, arteriosclerosis, sinus empyema, echinococcus orbitae and basal meningitis. It is hardly conceivable that the regenerating fibers would be misdirected in all these cases in exactly the same way and thus lead to exactly the same associated movements.

This ever present pattern of the associated movements which occurs after any lesion to the third or the seventh nerve anywhere along its course demands that one look for the genesis of such movements in the place of origin of these nerves—their nuclear structure.

16. Associated movements in the oculomotor or facial muscles, once established, remain for the duration of the patient's life. It is hardly necessary to cite from the literature, as reports are unanimous on this matter; suffice it to mention the case of Gowers [91] in which associated movements "were still considerable" twenty-five years after the attack. The second case in my series presents an unusual exception to the general rule that the associated movements in the

88. Hitzig, E.: Ueber die Auffassung einiger Anomalieen der Muskelinnervation, Arch. f. Psychiat. **3**:312 and 601, 1872.

89. von Michel, J.: Die Krankheiten der Augenlider, in Graefe, A., and Saemisch, T.: Handbuch der gesamten Augenheilkunde, ed. 2, Leipzig, Wilhelm Engelmann, 1908, vol. 5, pt. 2, p. 440.

90. Camison, A.: Un caso de pseudo-signo de Graefe, Rev. cubana de oto-neuro-oftal. **2**:235, 1933.

91. Gowers, W. R.: A Manual of Diseases of the Nervous System, ed. 2, Philadelphia, P. Blakiston's Son & Co., 1907, vol. 2, p. 243.

muscles innervated by the third nerve do not recover. Here a spontaneous and complete recovery took place, and this without any therapy. It must be assumed that, though extremely rare, the associated movements may regress completely, especially in cases of mild palsies; in some they do not appear at all. However, I have never seen or heard or read of a patient who has recovered from, or shown the least improvement in, associated movements after a lesion of the seventh nerve. The stubborn persistence of the postparalytic associated movements with palsies of the third and seventh nerves is in sharp contrast to the duration of the movements which follow anastomosis of the peripheral nerves. Here the resulting pronounced associated movements can be improved with exercise and therapy. With regard to hypoglossofacial and spinofacial anastomosis, Peet [92] stated: "Reeducation of the cortical centers seems to take place, as in many patients the associated movements practically disappear." There is no such therapy for the associated movements of the facial or oculomotor muscles; they remain permanent.

17. If and when after an injury to a nerve regenerating fibers go astray, this could, evidently, produce associated movements only in the area of the muscles supplied by this nerve. However, many a feature of a seventh or a third nerve palsy seems to indicate that the lesion must have spread centrally, far beyond the peripheral nerve trunk and its nucleus. Associated movements have been observed after a peripheral seventh nerve palsy which seem to indicate that the connection between this nerve and the fifth was involved. Jolly [93] observed in a case of bilateral peripheral facial palsy the following peculiar associated movement: Whereas the patient was completely unable to lift the corner of his mouth, he could perform this movement on the left side the moment he clenched his teeth tightly. Here a contraction of the masseter muscle brought about an associated movement from the fifth to the seventh nerve. Oppenheim [40] observed a palsy of the right side of the face in which a jerking of the lower jaw to the left occurred simultaneously with the blinking of the left eye. This is an associated movement from the seventh to the fifth nerve. Associated movements of the same kind were observed by Ornsteen [94] in a patient with acute polyneuritis and facial diplegia. In this case each voluntary and involuntary movement of the eyelid

92. Peet, M. M.: The Cranial Nerves, in Lewis, D.: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1944, vol. 12, chap. 2, p. 63.

93. Jolly: Ueber einen Fall von doppelseitiger Facialislähmung, Deutsche med. Wchnschr. **26**: 173, 1900.

94. Ornsteen, A. M.: Palpebromandibular Synkinesis in a Patient with Acute Polyneuritis and Facial Diplegia, Arch. Neurol. & Psychiat. **34**:625 (Sept.) 1935.

was synchronously associated with an involuntary short, sharp movement of the jaw. Here, again, one is dealing with an associated movement from the facial to the fifth nerve in a case of peripheral facial nerve palsy. The phenomenon was not reversible; i. e., the movement of the mandible did not cause involuntary associated movement of the eyelid. However, in the case of peripheral facial palsy described by Alajouanine and associates [95] the associated movements of the seventh and the fifth nerve were mutual and reversible. Kramer [96] observed associated movements in the paretic facial muscles on innervation of the facial muscles on the normal side. A case of a physiologically interesting congenital condition was reported and illustrated by Lyle.[97] In a middle-aged woman the face and eyes were perfectly normal at rest; but when the patient retracted the corners of her mouth this voluntary movement caused the right eye to proptose and roll downward and slightly outward, and both lids to retract. Lyle assumed that the fibers between the facial and the oculomotor nerve made a wrong "hook-up." Some "hook-up" must certainly have been at play, but it is hardly possible to assume that both nerves had intruded into each other's pathways in their peripheral course.

After oculomotor palsy, too, associated movements which trespass on the area of this nerve can be observed. Suffice it to mention the well known jaw-winking phenomenon of Marcus Gum. Here, after a third nerve palsy with ptosis, we have associated movement from the fifth to the third nerve: elevation of the upper lid on movement of the jaw. This, by the way, is undoubtedly a phylogenetically archaic phenomenon, seen in fish physiologically. A remarkable instance of associated movements with third nerve palsy was described by Ascher.[98] Here the Marcus Gunn phenomenon appeared and disappeared in the course of syphilitic palsy of the third nerve. A 44 year old patient with syphilis had complete palsy of the right third nerve. After the palsy had existed for six months and the patient had received intensive antisyphilitic treatment, he noticed that the upper lid, previously unmovable, rose automatically on opening the mouth and on chewing. After one week, this phenomenon dis-

95. Alajouanine, T.; Thurel, R., and Albeaux-Fernet, M.: Paralysie faciale périphérique avec dissociation des activités volontaire et réflexe, Rev. neurol. **1**:398, 1934.

96. Kramer,[4] p. 351.

97. Lyle,[38] p. 91.

98. Ascher, K.: Auftreten und Verschwinden des Marcus Gunnschen Kiefer-Lid-Phänomens während des Rückgangs einer luischen Ptosis, Med. Klin. **33**:1259, 1937.

appeared and the upper lid regained its voluntary motility, but other oculomotor muscles remained paralyzed. Associated movements are further observed with third nerve palsy between muscles of this nerve and the facial muscles, for instance, the musculus frontalis. Very common in cases of third nerve palsy are associated movements between the third and the sixth nerve. This may occur with the sixth nerve also being involved or remaining intact. Thus, the associated movement of raising the eyelid on abduction of the eye is not uncommonly observed. This is wrongly called Friedenwald's sign. It was described by Phillips [99] in 1887, whereas Friedenwald [100] described it in 1893.

A physiologically significant observation along this line was briefly reported by Goodhart and Balser.[101] In their case a man with sequelae of epidemic encephalitis showed the unusual phenomenon of inability to open the voluntarily closed eyes; in order to do so, he was obliged to carry out a movement of extreme hyperextension of the head. Here, again, there is associated movement, namely, from the muscles which retract the head to the levator palpebrae. This shows once more how easily and readily the movements of the levator palpebrae are linked with those of remote muscles.

Needless to say, in all these instances in which associated movements appear with seventh or third nerve palsy which involve areas beyond the distribution of these nerves, it is impossible to incriminate misdirection of fibers. The fibers of the third and the seventh nerve could not possibly grow by mistake into compartments of the fifth and the sixth nerves, or vice versa. To explain these conditions, it must be assumed that the underlying cause acts centrally rather than on the trunk of the nerves, as set forth by the hypothesis of misdirection.

Comment.—After all that has just been said in criticism of the hypothesis of the misdirection of regenerating nerve fibers, it must be admitted that some of these seventeen points may be weak, some argumentation not quite convincing, some statements neither proved nor possible to prove at present. However, taken as a whole, these points convey the definite impression that the hypothesis of misdirection of fibers as an explanation for associated movements in the muscles innervated by the third and seventh nerve is untenable, despite the fact that a galaxy of such names as Babinski, André Thomas, Bielschowsky and Fulton is behind it.

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99. Phillips, S.: Associated Movement of Upper Lid with Movement of Eyeball, Tr. Ophth. Soc. U. Kingdom **7**:306, 1887.

100. Friedenwald, H.: Movements of the Upper Eyelid Associated with Lateral Movements of the Eyeball, Arch. Ophth. **22**:349, 1893.

101. Goodhart, S. P., and Balser, B. H.: Neurological Cinematographic Atlas, New York, King's Crown Press, 1944, p. 48.

ASSOCIATED MOVEMENTS AFTER LESIONS OF THE THIRD OR THE SEVENTH NERVE AS COMPARED WITH THOSE AFTER LESIONS OF THE PYRAMIDAL TRACTS

Another approach to this problem is the comparison of associated movements occurring after injury to the third and seventh nerve with those which occur after lesions of the pyramidal tracts. Walshe [102] regarded the associated movements of hemiplegia as postural reactions, as variations in muscle tone attitude rather than as movements in the strict physiologic sense. They were, in his opinion, tonic or postural reflex reactions allied "to the tonic neck and labyrinthine reflexes of Magnus and de Kleijn." But the term "associated movements," so widely accepted (*Mitbewegungen* of the German, *mouvements associés* of the French), is more in keeping with the phenomena as they appear clinically. The associated movements in the territory of the cranial nerves can be defined in the same way as Riddoch and Buzzard [103] defined associated movements in hemiplegia:

> . . . automatic activities which fix or alter the posture of a part or parts when some other portion of the body is brought into action either by voluntary effort or by artificial reflex stimulation.

Whether occurring in the face or in the extremities, they must, clinically, be regarded as similar, and it is most interesting to note that as far back as 1896 Friedenwald [77] said of associated movements acquired with third nerve paralysis that they "belong in the same category as those associated movements observed in hemiplegia." This profound remark of Friedenwald's remained completely unnoticed.

There are various kinds of associated movements which occur with lesions of the pyramidal tract. They may be generalized, producing an exaggeration of the hemiplegia posture, or they may be symmetric, imitating on the paretic side the movements performed on the normal one. They may be coordinated and consist of synergic movements in muscles of an extremity other than in those directly innervated. The French called them *syncinésies de coordination.* There are numerous instances of such coordinated associated movements. Take, for instance, the so-called tibialis sign of Strümpell: On voluntary bending of the outstretched leg at the hip joint, a simultaneous involuntary and insuppressible dorsiflexion and supination of the homolateral foot ensues. This is an associated movement of the same kind which occurs with oculomotor palsy when the patient,

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102. Walshe, F. M. R.: On Certain Tonic or Postural Reflexes in Hemiplegia, with Special Reference to the So-Called "Associated Movements," Brain **46**:1, 1923.

103. Riddoch, G., and Buzzard, E. F.: Reflex Movements and Postural Reactions in Quadriplegia and Hemiplegia, Brain **44**:397, 1921.

moving the paretic eye inward, simultaneously raises his paretic upper lid, a movement which occurs completely automatically and is not suppressible. It is remarkable that many diagnostic signs of hemiplegia (often called reflexes) are based on associated movements. To list a few: Raïmiste's abduction and adduction sign consists of involuntary abduction or adduction of the spastic leg on corresponding movement of the normal leg against resistance. Babinski's trunk sign consists of flexion of the thigh on attempting to rise from the supine position; this is an associated movement of the flexors of the thigh on movement of the trunk muscles. In Néri's leg sign, bending of the knee is associated with bending of the thigh. Saethre's sign consists of abduction of the leg associated with flexion of the hip and knee joints. Strümpell's pronation sign is a pronation of the forearm on bending of the elbow. Wartenberg's thumb sign consists of an opposition, adduction and flexion of the thumb on bending the fingers against resistance. Souques' phenomenon of the interosseus muscles consists of extension and abduction of the fingers on raising the arm. All these signs are associated movements which, in my opinion, constitute the fundamental phenomenon of the pyramidal lesion.

Both the associated movements in the extremities after a lesion of the pyramidal tract and the associated movements seen after lesions of the third and seventh nerves dominate the clinical picture. They not only have a striking similarity at the first glance but reveal a close relationship on detailed examination. In both instances the essential stimulus is a voluntary or an involuntary contraction of muscles. Actual excursion of movement of the primary contracted muscle is not necessary; only a strong tonic muscular contraction is needed. Some degree of hypertonus is an essential preliminary to the development of associated movements in both areas; some degree of hypertonus is distinctly seen also in the facial muscles. In both conditions a movement which cannot be performed on voluntary stimulation of the muscle can be carried out as an associated movement on direct stimulation of other muscles. In both conditions movements which appear as associated movements may exceed the normal response. They are stereotyped, constant in their form, do not vary under the modes in which they may be produced and are resistant to therapy.

SYMPTOMS OF LESIONS OF THE THIRD OR THE SEVENTH NERVE AS COMPARED WITH SYMPTOMS OF LESIONS OF THE PYRAMIDAL TRACT

In comparing the sequelae of a lesion of the pyramidal tract with those of a lesion of the third or seventh nerve, one may say that the two conditions are characterized by associated movements which are,

to say the least, similar. These two conditions have—strange as it may seem at first glance—features in common in addition to these associated movements. The features may be summarized as follows:

1. There is weakness of the affected muscles.

2. There is contracture of the muscles. These contractures are self evident in the facial muscles. They are present when associated movements are observed. But muscular contractures occur, though seldom, also in cases of paralysis of the third nerve. I mean, of course, not paralytic contractures of the unopposed muscles of the unaffected nerves but contractures of the oculomotor muscles proper. Cohn and Isakowitz [104] showed that contractures may occur in the course of ophthalmoplegia in the paretic ocular muscles. In their case of ophthalmoplegia due to syphilitic basilar meningitis there was a pronounced contracture of the levator palpebrae. Coppez,[8] too, spoke of contracture in the affected oculomotor muscles and cited Behr. The readiness with which the levator palpebrae reacts with contraction to many outside impulses and the occasionally abnormal range of this contraction speak for a latent state of spasticity.

3. There are spontaneous hyperkinesias both in spastic extremities after a lesion of the pyramidal tract and in partially recovered paretic muscles innervated by the third or the seventh nerve. With regard to the seventh nerve, it is of course extremely difficult to distinguish these spasmodic contractions from associated movements subsequent to the blinking of the eye. But there is ample evidence that, besides these associated movements, there are postparalytic facial spasms, some of which are rhythmic. Gowers,[105] having discussed the postparalytic movements of the seventh nerve, stated that "in many cases another symptom is added after a time—spontaneous twitchings, isolated spasmodic contractions, recurring at irregular intervals, and affecting chiefly the zygomatici." Lipschitz, the father of the hypothesis of misdirection, began his monograph devoted to the postparalytic phenomena after seventh nerve palsy by saying that he was going to explain three points: (1) associated movements, (2) spontaneous contractions which occur from time to time in the paralyzed area and (3) the exaggeration of reflexive irritability in the formerly paralyzed half of the face. Ballance [106] claimed that the spontaneous contractions of the muscles of the face in man—when recovery from paralysis of the face is long delayed and more or less imperfect—are

104. Cohn, T., and Isakowitz: Kontrakturen paretischer Augenmuskeln, Deutsche med. Wchnschr. **52**:1473, 1926.

105. Gowers,[91] p. 242.

106. Ballance, C.: The Operative Treatment of Facial Palsy with Observations on the Prepared Nerve Graft and on Facial Spasm, J. Laryng. & Otol. **49**:709, 1934.

the common and permanent result of long-continued medical treatment. It is not quite certain what he means here by "spontaneous contractions." In another work (Ballance and Duel [107]) the so-called spontaneous spasms are certainly considered as associated movements. In any case, it is completely erroneous to assume that spasmodic contractions or associated movements after facial palsy have anything to do with treatment. They are part and parcel of the postparalytic phenomena, and treatment neither produces them nor influences them essentially.

Such spontaneous involuntary spasmodic contractions occur also in paralyzed muscles of the third nerve. In one of the first papers on associated movements after oculomotor paralysis, Fuchs,[7] in 1893, described a case (case 3) in which rhythmic contractions of the levator occurred. Von Bechterew [108] was one of the first to describe, in a case of third nerve palsy of syphilitic origin, a rhythmic spasm of the levator. Of the recent publications on this subject, that of Bollack [109] may be mentioned. The so-called cyclic oculomotor nerve paralysis, about which a voluminous ophthalmologic literature exists, probably belongs here. In this condition there is a paralysis of the oculomotor nerve with alternating phases of clonic spasm and relaxation of its muscles. Reference might be made here to Bielschowsky's [52] review of this subject. He localized the lesion in the region of the nucleus of the third nerve. A remarkable case of this kind, in which the oculomotor nerve palsy was congenital, was described by Kubik.[110] In a case reported by Stein [111] the palsy was acquired early in life. Some observers stress the automatic and rhythmic character of the movements. Walsh and King [60] described 1 of their cases as follows:

> The patient, a man of 23, had exhibited what appeared to be complete oculomotor nerve paralysis on the left for fifteen years. At irregular intervals the left lid surged open and remained elevated for a few seconds or for as long as several minutes. . . . The elevation might occur spontaneously or might be produced by bathing of the face in cold water. The patient stated that elevation of the lid invariably appeared when he lost his temper or became interested in an attractive member of the opposite sex.

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107. Ballance, C., and Duel, A. B.: The Operative Treatment of Facial Palsy, Arch. Otolaryng. **15**:1 (Jan.) 1932.

108. von Bechterew, W.: Ophthalmoplegie mit periodischer unwillkürlicher Hebung und Senkung des oberen Lides, paralytischer Ophthalmie, und einer eigenartigen optischen Illusion, Deutsche Ztschr. f. Nervenh. **16**:209, 1900.

109. Bollack, J.: Rétraction spasmodique de la paupière supérieure consécutive à une paralysie de la troisième paire, Rev. d'oto-neuro-opht. **13**:452, 1935.

110. Kubik, J.: Ueber kongenitale Okulomotoriuslähmung mit erworbener zyklischer Innervation des inneren Okulomotoriusastes des Levator palp. sup., Klin. Monatsbl. f. Augenh. **73**:131, 1924.

111. Stein, R.: Okulomotoriuslähmung mit zyklischer Innervation der inneren Augenmuskeln, Med. Klin. **27**: 350, 1931.

With lesions of the pyramidal tract there are, too, such involuntary spasmodic contractions—for instance, in patients with transverse lesions of the spinal cord. A rhythmic flexor withdrawal reflex, or a rhythmic Babinski toe sign, and alternating flexion and relaxation of the spastic extremities are observed. These occur with slight or with extensive movement of the extremities. Walshe [112] stated that involuntary flexor spasms occurring in cases of paraplegia in flexion are "characterized by complete intermissions of the spasm, which result in the production of alternating flexion and extension movements."

The spasmodic contractions in the paretic facial or oculomotor muscles may be considered, to say the least, as an analogue of the spasmodic contractions occurring in spastic extremities. In both instances they occur either on peripheral stimulation or without it, or perhaps on some stimulation the nature of which cannot be determined. In both instances these spasmodic contractions may be rhythmic, but they are always completely involuntary.

4. In both conditions there are certain definite patterns for the associated movements, as well as for the spasmodic contractions. They always recur in a stereotyped manner.

5. There is hyperreflexia in both conditions. Strümpell [113] emphasized the exaggerated reflexive irritability after facial nerve palsy, as did Hitzig.[88]

6. In both conditions the associated movements, the contractures, the spasmodic contractions and the increased reflexive activity are permanent and not amenable to treatment.

7. The associated movements can appear on the basis of a congenital defect and are not directly dependent on the degree of palsy.

8. The hyperkinetic manifestations are independent both of the nature and of the location of the lesion.

9. In both conditions there is an incubation period between the occurrence of the lesion and the appearance of the hyperkinetic phenomena.

10. The motility shows a phylogenetic regression in both conditions. Primitive mass movements are brought to light, and phylogenetically older muscles come into play. The highest, and later acquired, functions are particularly disturbed, especially those of greater complexity and greater differentiation. A dedifferentiation takes place. This is self evident in a lesion of the pyramidal tract, but the same is true also for facial nerve palsy. It is a well established fact that the facial muscles

112. Walshe, F. M. R.: The Physiological Significance of the Reflex Phenomena in Spastic Paralysis of the Lower Limbs, Brain **37**:*269*, 1914.

113. Strümpell, cited by Oppenheim,[5] p. 735.

started phylogenetically as a single unit but have undergone a differentiation in the course of development. In facial palsy the associated movements show a phylogenetic regression, exactly as with a lesion of the pyramidal tract; the facial muscles have lost their ability to contract individually; a mass movement appears instead.

As to the muscles innervated by the third nerve, it may be assumed that the great tendency of the levator palpebrae and of the rectus internus toward associated movements has some phylogenetic significance. They are teleologically the most important muscles for the act of gazing, since the prerequisite for any visual act and for fixating a near object is opening of the eye and inward movement of the eyeball. These phylogenetically older movements are preserved and are ready to spring into action on any stimulus. These movements constitute what could be called the "fixation reflex," in analogy to the "flexor withdrawal reflex."

Thus, in the light of this confrontation, phylogenetically old movements come to the fore, both with lesions of the pyramidal tract and with those of the seventh or third nerve. According to this view, the levator palpebrae and the rectus internus show increased reflexive activity with a third nerve palsy, exactly as the flexors of the lower extremities do with transverse lesions of the spinal cord.

Walsh and King [60] and Ford and Woodhall [58] gave different explanations of the striking fact that the levator palpebrae and the rectus internus show such increased reflexive activity and such a strong tendency toward associated movements. "When an effort is made," said Walsh and King, "to move the eye in any direction, impulses flow at the same time into all the muscles innervated by the third nerve. Movement up or down does not occur, since the superior and the inferior rectus muscle contract together and the pull is balanced." "The tendency of the eye," said Ford and Woodhall, "to be adducted when other movements are attempted may be due to the fact that the action of the internal rectus is not opposed by synchronous contraction of the external rectus." This explanation is on a purely mechanical basis: An impulse sent to any of the muscles innervated by the third nerve radiates to all muscles of this nerve and brings about their simultaneous contraction. Those muscles innervated by the third nerve which are opposed by other muscles of this nerve will be counterbalanced, and no visible movement will result on their simultaneous innervation. But those muscles controlled by the third nerve, which are opposed by muscles not innervated by other branches of the third nerve, will effect, through their unopposed action, displacement of the bulbus or of the eyelid.

Against this hypothesis the following weighty objections may be raised: 1. The usual associated movements may occur even when there

is no palsy of any muscle. 2. The levator palpebrae muscle is unopposed by any muscle innervated by the third nerve. But there are pathologic associated movements from the rectus internus to the levator palpebrae, whereas there are none from the rectus superior to the levator palpebrae. The latter can be proved by the fact that when the patient closes his eyes and is asked to look upward the levator palpebrae does not move. Thus, the unopposed levator palpebrae reacts differently according to whether the rectus internus or the rectus superior is innervated. 3. There are no, or no distinct, associated movements from the levator palpebrae to other muscles. In other words, the impulse sent to the levator does not radiate to all other muscles innervated by the third nerve. 4. The single oculomotor muscles are by no means equally affected, and their action consequently cannot be completely balanced. Partial movements are still possible, and in some muscles more so than in others. 5. Associated movements are greater on looking downward than on looking upward. This, again, shows that some other factor is at play here, not merely an even flow of impulses through all branches of the third nerve when a single branch has been stimulated. For all these reasons it appears that the explanation of Ford and Woodhall is not tenable.

The foregoing discussion serves to stress one fact: the striking similarity between the condition due to lesions of the pyramidal tracts, as seen in cases of spastic paralysis, and the condition in the muscles of the third or the seventh nerve after partial recovery from palsy.

ASSOCIATED MOVEMENTS AFTER LESIONS OF THE THIRD OR THE SEVENTH NERVE IN THE LIGHT OF THE RELEASE HYPOTHESIS OF HUGHLINGS JACKSON

Hughlings Jackson looked at the phenomena of spastic paralysis as release phenomena (*phénomène de relâchement, de libération,* of the French; *Enthemmungssymptom,* of the German). This brilliant hypothesis has proved extremely fruitful in the whole field of neurology, especially in the interpretation and elucidation of the phenomena that occur with lesions of the pyramidal tract. After what has been said here on the symptomatology of third and of seventh nerve palsy, it is natural to attempt to apply Jackson's hypothesis to these phenomena as well. It, then, must be assumed that an "escape from control" as it occurs in case of a lesion of the pyramidal tract takes place also with lesions of the third and the seventh nerve. All the phenomena seen with the latter, i. e., associated movements, muscle contractures and hyperreflexia, with their permanency and elements of phylogenetic retrogression, can be explained just as readily as they are with lesions of the pyramidal tract. This hypothesis will also explain the difficulty encoun-

tered in the treatment of these conditions, since it is known how unmanageable is any condition which is a release phenomenon.

There is one serious obstacle to the attempt to extend Jackson's hypothesis to the phenomena due to a central or a peripheral lesion of the third or the seventh nerve. The third and seventh nerves are regarded as purely peripheral nerves, as is any spinal nerve originating from the anterior horns of the spinal cord. Also, the nuclei of the third and seventh nerves are looked on as corresponding to a nucleus of the anterior horn. However, this viewpoint calls for a change. The peripheral neurons of the third and seventh nerves are different. The motility in these nerves is regulated by centers which might be divided into nuclear, supranuclear, subcortical and cortical centers. It must be assumed that, in contrast to the spinal nerves, the nuclear and closely neighboring supranuclear centers are more important for the movements of the muscles controlled by the third and seventh nerves than the anterior horns are for the movements of the muscles of the extremities. The nuclear and supranuclear mechanisms of these two nerves are far more complicated and more independent of cortical and subcortical control than is the mechanism of a spinal nerve. The nuclear and supranuclear mechanisms of the third and seventh nerves might represent for the respective muscles some combination of a pyramidal and a peripheral system, with the cerebral cortex exerting only a slight influence. The significance which the pyramidal tract, the first neuron, has for the muscles of the extremities, the supranuclear and nuclear centers of the third and seventh nerves have for the ocular and facial muscles; a lesion of these centers produces phenomena analogous to the spastic paralysis seen with lesions of the first neuron. In this connection it is worth while to mention "that there may be a localization of movement rather than individual muscles in the oculomotor nucleus" (Clark [114]), exactly as is found in the cortex.

An injury to this peripheral, nuclear or supranuclear mechanism of these nerves has the same effect on the movement of the eyes and face, respectively, as a lesion of the pyramidal tract has on the movements of the extremities. The lesion "knocks out" the frail, phylogenetically young mechanisms and thus releases phylogenetically older mechanisms, with their tendency toward associated movements. Jackson propounded the theory that the highest and most lately developed functions suffer first in the process of disease, that the removal of the inhibition of these highest centers results in the uncontrolled action of the lower centers. The assumption of existence of nuclear and supranuclear centers for the third and seventh nerves is of course highly hypothetic. It might

114. Clark, W. E. L.: The Mammalian Oculomotor Nucleus, J. Anat. **60**:427, 1926.

be less so if it is assumed that there exist in the nuclei types of cells of diversified physiologic dignity, as, for instance, in the striatum (Hunt [115]). The nuclei might contain phylogenetically younger, less resistant, physiologically highly differentiated cells, on the one side, and phylogenetically older, more resistant, physiologically less differentiated cells, on the other. An injury to the third or the seventh nerve at any point in its course damages the weaker cells first, and associated movements result on partial recovery. When both types of cells are damaged, no recovery and no hyperkinetic phenomena ensue.

It is of course striking how readily associated movements appear in the area of the third and seventh nerves on the slightest injury. This is due to the fact that the centers of this area, as of the whole area of the cranial nerves, carry, buried in their depths, a much more elaborate mass movement anlage than does any spinal nerve center. This area is innately a playground for mass movements of many types. The muscles of the eye and face have, even under normal conditions, a great tendency toward associated movements—this is especially true of the ocular muscles, and particularly of the levator palpebrae. Some of these associated movements in the area of the third and seventh nerve are not directly pathologic but appear on the slightest deviation from the norm. They are atavistic, dormant. Their inhibitory, restraining mechanism is so frail, they are kept at bay so loosely, that they become discernible on the slightest provocation. They appear also—and not uncommonly—as congenital anomalies. Suffice it to mention here the Marcus Gunn phenomenon. Some of these associated movements are on the physiologic borderline and appear in infants and especially in persons with motor infantilism, and they may appear even in normal persons. The degree to which these tendencies toward associated movements are suppressed by the higher centers varies much from person to person. Darwin [116] pointed out that some short-sighted people who contract their orbicularis oculi muscle when looking at distant objects raise their upper lip at the same time. This is the most typical pathologic associated movement seen with lesions of the seventh nerve. Coppez [117] made an interesting compilation of all the associated movements observed in the ocular muscles, which shows their tremendous variety under normal, as well as under pathologic, conditions. All

115. Hunt, J. R.: Progressive Atrophy of the Globus Pallidus, Tr. Am. Neurol. A. **43**:104, 1917.

116. Darwin, C., cited by Collier, D. J., in Discussion on the Limitations of Operative Treatment in Traumatic Facial Paralysis, Proc. Roy. Soc. Med. **34**: 575, 1941.

117. Coppez, H.: Essai de classification de quelques syncinésies oculaires, Rev. d'oto-neuro-ocul. **10**:12, 1932.

this makes it understandable why the slightest lesion in the area of the ocular and facial muscles brings to light associated movements.

The hypothesis presented here implies that the associated movements and other postparalytic motor manifestations in the areas of the third and seventh nerves are release phenomena, due to involvement of centers in the brain stem. This hypothesis must now stand a severe test; i. e., it must answer the following question: How is it possible that these centers suffer when the lesion affects the trunk, or even the end branches, of the third or the seventh nerve? The answer is: *réaction à distance,* as the French call it. As far back as 1893, Darkschewitsch and Tichonow [118] demonstrated pathologic changes in the nucleus of the facial nerve after damage to the peripheral nerve. In 1896 Flatau [119] found definite degeneration in the nucleus of the facial nerve in a case of peripheral palsy due to tuberculous otitis. Vespa [120] observed degenerative changes in this nucleus, especially in its dorsomedial part, in a case of peripheral facial palsy of long standing with—and this is of particular interest—contractures and associated movements, as did Mirallié.[120a] The same changes have been found with experimental lesions of the seventh nerve. The medullary nucleus of the facial nerve, stated Sullivan,[121] does show histologic change in monkeys whose facial nerve has been cut and allowed to undergo degeneration for varying periods before being repaired. As to the third nerve, Brouwer [66] described retrograde degeneration—though slight—in its motor nucleus after peripheral injury. De Gutiérrez-Mahoney [122] mentioned observations made by the method of retrograde reaction following intracranial division of the oculomotor nerve in the monkey, baboon and chimpanzee. The retrograde reaction (chromatolysis) was noted in the homolateral motor cells and in some cells of the central nucleus of Perlia. Van Gehuchten and van Biervliet [122a] reported similar experiments on rabbits. Wilson [123]

118. Darkschewitsch, L., and Tichonow, S.: Zur Frage von den pathologisch-anatomischen Veränderungen bei peripherer Facialislähmung nichtspecifischen Ursprungs, Neurol. Centralbl. **12**:329, 1893.

119. Flatau, E.: Pathologisch-anatomischer Befund bei einem Fall peripherischer Facialislähmung, Neurol. Centralbl. **15**:718, 1896.

120. Vespa, B.: Studio sulle alterazioni del nucleo bulbare del faciale, in caso di antica paralisi periferica di questo nervo, Riv. quindicin. di psicol. **2**:267, 1898-1899.

120a. Mirallié, C.: Paralysie faciale périphérique; Autopsie, Rev. neurol. **14**:702, 1906.

121. Sullivan, J. A., in discussion on Fowler, E. P.: Abnormal Movements Following Injury to the Facial Nerve, J. A. M. A. **113**:1003 (Sept. 9) 1939.

122. de Gutiérrez-Mahoney, C. G., in discussion on Bender and Weinstein,[68] p. 51.

stated: "The view that local irritation of a nerve-trunk causes some *réaction à distance* on the nucleus is not physiologically impossible." Elsewhere he stated: "The underlying process in Bell's palsy consists of a simple parenchymatous toxi-degeneration, with *réaction à distance* on the nucleus." It is thus understandable that a lesion anywhere in the area of the third or the seventh nerve influences the nucleus, thus damaging the function of the frail, phylogenetically young superstructure, which controls fine, isolated movements. This superstructure is responsible for the differentiation of muscle function. If it is damaged, a "dedifferentiation" results, which is the essence of associated movements.

The many objections raised here previously against the hypothesis of misdirection of fibers can easily be met in the light of the hypothesis of release phenomena, which places the origin of the associated movements not at the site of the peripheral lesion but in the nuclear structure, which is influenced by the distant lesion. The associated movements occur, then, only in those lesions of the nerve which are severe enough to influence the nucleus from a distance. The hypothesis of release phenomena does not deny the possible misdirection of fibers, especially after surgical injury to a nerve. However, it does not hold this misdirection responsible for permanent associated movements and regards the role of misdirection as temporary or, at the most, as negligible in comparison with the tremendous impact engendered by the loss of control from the higher centers. Associated movements are independent of the nature of the lesion and appear whether the lesion is surgical or nonsurgical, local or diffuse, since any lesion in the area of the third or the seventh nerve may, in its retrograde action, influence the nucleus, damage it and thus promote loss of control on the part of the higher, extremely susceptible, sensitive centers. This hypothesis places the third and seventh nerves in a category distinct from the spinal nerves. In view of the innate tendency of the normal third and seventh nerves—and of all cranial nerves—toward associated movements, active or dormant, and in view of their phylogenetic development, such an assumption is by no means unreasonable. In the light of the hypothesis of the release phenomena, it is understandable why neighboring compartments do not intermingle readily, as had to be assumed on the basis of the hypothesis of misdirection, and why the participation of this or that muscle in the associated movements is not dependent on its particular response to voluntary innervation. The salient point is that the selec-

122a. van Gehuchten and van Biervliet: Le noyau de l'oculomoteur commun, 16, 19 et 21 mois après la résection du nerf, Névraxe **2**:207, 1901.

123. Wilson, S. A. K.: Neurology, London, Edward Arnold & Co., 1940, pp 405 and 1639.

tion—so to speak—of the muscles for their participation in the associated movements is not decided on in the periphery, at the site of the damage and according to the lawless sprouting of the regenerating fibers, but in the nuclear mechanism, and here according to the phylogenetic point of view, in conformity with the law of survival of the fittest and simplest. The nature of the injury, the state of the nuclear mechanism and the actual damage to the "final common path" may, of course, influence the clinical manifestations of the associated movements, but only to a minor degree. Their tendency is dominant, and they assert themselves despite all obstacles.

The predominant participation of the levator palpebrae and the rectus internus in associated movements is easily explained on the basis of the assumption that they are phylogenetically older muscles. They subserve the most primitive movements necessary for the visual act: opening of the eye and turning the eye inward to fixate a near object. These muscles can be compared to the flexors of the leg which subserve the primitive reflex of withdrawal of flight. In the manifestations of spinal automatism, the action of the flexors of the legs is also predominant. In both conditions a loss of control accounts for the prominence of these movements. Both with lesions of the third and seventh nerves and with lesions of the pyramidal tract there is no parallelism between the ensuing palsy and the tendency toward associated movements. The latter may be very marked though the palsy be minimal. With both lesions associated movements can occur as a congenital anomaly, as a persistent motor defect. Some kind of motor infantilism may be present without, or with only a slight, impairment of the motor power of the affected muscles. Associated movements in the facial or oculomotor muscles need time for their development—time until the peripheral injury affects the nucleus from a distance, and until the diaschisis passes over. It is quite possible to assume that the "incubation period" within which the lesion could influence the nucleus in retrograde action would be shorter than the time it would take for the fibers to grow from the point of lesion to the periphery. Since the hypothesis of release phenomena places the genesis of associated movements in the nucleus, their appearance with lesions of the nucleus is quite understandable. The nuclear and supranuclear mechanisms of the third and seventh nerves are so delicate, their phylogenetically younger structure is so fragile, they are so easily deranged in their function, that associated movements which follow the damage to these mechanisms appear regardless of the nature or location of the lesion, unless, of course, the lesion is so mild and the damage so slight and easily repaired that no retrograde action on the nucleus takes place, or unless the entire mechanism of the third or the seventh nerve is destroyed, as in cases of severe acquired lesions

or of congenital malformations. In the latter condition the palsy is complete and no associated movements appear. The same is true of lesions of the pyramidal tract; there are no hyperkinetic phenomena of any kind if the whole motor system is destroyed. According to Jackson's theory, destructive lesions do not cause positive symptoms, as living and active tissue is required for their production. As there are numerous conditions with congenital insufficiency of the pyramidal tract, so also there may be congenital insufficiency in the motor mechanisms of the third and seventh nerves leading to associated movements, and to these only. Cyclic or rhythmic oculomotor palsy could be explained in the light of this hypothesis as being due to sudden discharge in the higher centers of the third and seventh nerves, in the brain stem. This leads to release phenomena on the part of the lower centers. This is comparable to what is seen in cases of epilepsy, especially of so-called autonomic epilepsy. The constant and persistent, almost monotonous, pattern seen with associated movements of the third and seventh nerves, and also with lesions of the pyramidal tract, is due to unrestricted activity of preserved and comparatively healthy, undamaged nerve centers, which continue to act according to their own characteristic physiologic function. They remain, therefore, for life—unchanging and unchangeable—and are not amenable to therapeutic influence. This is true of flexor spasm seen with pyramidal lesions, of associated movements occurring with palsies of the third and seventh nerves, as well as of any release phenomena referable to other systems of the cerebrospinal axis. This general rule does not exclude the fact that in rare instances the damage inflicted by the peripheral lesion to the central station may be so mild that spontaneous recovery leading to the cessation of the associated movements can and does take place. This occurred in case 2 of this series which, so far as I can discover, stands alone. But it can also be assumed that these temporary associated movements, occurring during the process of recovery of an injury to the third or the seventh nerve, are not so rare. They escape the notice of both the patient and the physician because of their mildness and transient character.

It is easily understandable that, because of the intimate connection between the motor mechanisms of all the cranial nerves, and by virtue of the very strong natural, inherent tendency toward associated movements of all the muscles innervated by the cranial nerves, a disturbance in one necessarily brings about a disturbance and release phenomena in others. Thus, associated movements between muscles of the oculomotor and the trigeminal nerves can be explained. The remarkable frequency with which associated movements of the facial muscles are found in cases of cryptogenic hemifacial spasm points to a common site of origin and

reminds one of conditions due to damage of the pyramidal system in which pathologic associated movements may exist but in which voluntary movements are little affected.

The hypothesis propounded here regarding the physiology of the associated movements of the facial and oculomotor muscles places the origin of these movements not in the nerve trunk at the site of the lesion, where misdirection of fibers could have taken place, but centrally, in the nucleus—in the nuclear or supranuclear mechanism. This is practically a regression to the old theories promulgated by Hitzig [88] (1872), Fuchs [7] (1893), Gowers [124] (1895), Remak [125] (1898), Myerson [85] (1920) and others, who assumed "a state of irritation" in the nucleus of the third and the seventh nerve, respectively. This theory was recently revived for the seventh nerve by Bittorf [75] and by Sullivan.[126] It is interesting to note in this connection that Stein [111] regarded cyclic oculomotor palsy as an isolation phenomenon, the preserved isles of the nucleus being isolated from supranuclear influence and displaying their own automatism. The only difference between the hypothesis propounded here and that of older authors is the view that the "state of irritation" is due to release of control.

GUSTOLACRIMAL REFLEX

After partial recovery of the seventh nerve palsy, not only pathologic motor phenomena—which are the subject of this paper—but pathologic vasomotor and secretory phenomena appear. For these, too, misdirection of regenerating secretory fibers has been regarded as "the simplest and most logical explanation" (Ford [127]). Russin [128] accepted Ford's view. Lyle [38] said cautiously: "A misdirection of regenerating fibers may be the cause." The most important of these vasomotor and secretory phenomena occurring after seventh nerve palsy are (1) the gustolacrimal reflex and (2) the auriculotemporal syndrome. Both are not uncommon but, oddly enough, are not even mentioned in such a detailed work as Wilson's "Neurology."

The pathologic gustolacrimal reflex, which is usually transient, appears only in cases of peripheral facial palsy. It consists of a flow

124. Gowers, W. R.: Clinical Lectures on Diseases of the Nervous System, Philadelphia, P. Blakiston's Son & Co., 1895, p. 115.

125. Remak, E.: Zur Pathogenese der nach abgelaufenen Facialislähmungen zurückbleibenden Gesichtsmuskelzuckungen, Berl. klin. Wchnschr. **35**:1144, 1898.

126. Sullivan, J. A.: A Modification of the Ballance-Duel Technique in the Treatment of Facial Paralysis, Tr. Am. Acad. Ophth. **41**:282, 1936.

127. Ford, F. R.: Paroxysmal Lacrimation During Eating as a Sequel of Facial Palsy (Syndrome of Crocodile Tears), Arch. Neurol. & Psychiat. **29**:1279 (June) 1933.

128. Russin, L. A.: Paroxysmal Lacrimation During Eating as a Sequel of Facial Palsy, J. A. M. A. **113**:2310 (Dec. 23) 1939.

of tears from the homolateral eye when gustatory stimuli reach the anterior part of the tongue. This reflex is called the "symptom of crocodile tears." It is a reflex from the chorda tympani through the nervus petrosus superficialis major to the nervus lacrimalis. This pathologic reflex appears with lesions of the facial nerve in the fallopian canal between the ganglion geniculi and the chorda tympani. It comes to light after the gustatory disturbances in the anterior two thirds of the tongue have disappeared. This reflex can be explained on the basis of a release of a phylogenetically old mechanism. The lacrimation on gustatory stimulation is an axon reflex usually suppressed by a normally functioning facial nerve. The old mechanism is still at play in man, but in a latent and restricted form. Suffice it to remember the wet, fatty eye of some persons while eating. This increased lacrimation occurs to a mild degree in normal persons also on urination and defecation. Under pathologic conditions this flow of tears may increase to so great a degree that real "micturition under tears" takes place. Since the arc of the axon reflex of lacrimation on gustatory stimulation ascends no higher than the ganglion geniculi, it is understandable that with a lesion of the facial nerve above this ganglion this reflex may be released, and thus intensive lacrimation on eating and chewing occurs. Kaminsky,[129] Kroll[130] and Bing[131] saw in the gustolacrimal reflex a release phenomenon.

AURICULOTEMPORAL SYNDROME

In the so-called auriculotemporal syndrome, seen after incomplete recovery from facial nerve palsy, and after some other conditions, there are redness and increased perspiration in the area corresponding approximately to that innervated by the auriculotemporal nerve. This occurs when the patient eats bitter or sour food. According to Kaminsky,[132] this phenomenon exists in latent form in normal persons and becomes conspicuous when lower peripheral centers and tracts are released. Guttmann,[133] too, looks on the auriculotemporal syndrome as a release phenomenon. He assumes that vasodilator and secretory fibers supplying the affected area of the face are released from sympathetic control through the primary lesion of the facial nerve. Thus,

129. Kaminsky, S. D.: Ueber das Syndrom der Krokodilstränen, Deutsche Ztschr. f. Nervenh. **110**:151, 1929.

130. Kroll, M.: Die neuropathologischen Syndrome, zugleich Differentialdiagnostik der Nervenkrankheiten, Berlin, Julius Springer, 1929, p. 222.

131. Bing, R.: Das Prinzip der "Enthemmung" in der Physiopathologie, Schweiz. Arch. f. Neurol. u. Psychiat. **32**:177, 1938.

132. Kaminsky, S. D.: Das "auriculo-temporale (Parotitis-) Syndrom" bei Syringomyelie, Deutsche Ztschr. f. Nervenh. **109**:296, 1929.

133. Guttmann L,: Die Schweisssekretion des Menschen in ihren Beziehungen zum Nervensystem, Ztschr. f. d. ges. Neurol. u. Psychiat. **135**:1, 1931.

sympathetic disturbances, both vasomotor and secretory, occurring after incomplete recovery from peripheral nerve palsy can also be viewed as release phenomena.

FACIAL SPASM

Going beyond the essential object of this study, namely, the pathophysiology of postparalytic phenomena of the third and seventh nerves, one finds it quite natural to apply the hypothesis of release to hyperkinetic phenomena of the seventh nerve which are not related to paralysis. Among them, the facial spasm is outstanding, especially with regard to its frequency. Wilson [134] stated:

> Facial spasm may be cryptogenic or symptomatic, non- or postparalytic, uni- or bilateral, partial or total, tonic, clonic, tonico-clonic, or fibrillary. Common though it is, both causation and pathogenesis are obscure, while pathological data are scanty and ambiguous.

It is the so-called cryptogenic, nonparalytic facial spasm which is considered here. The textbooks and monographs list an endless variety of pathologic conditions which can produce, secondarily, reflexively or otherwise, this facial spasm. The problem of causation is treated here exactly as in the case of trigeminal neuralgia. In medical practice it is different: None of the numerous theoretic causes can be uncovered in most cases. It is a matter of common experience that cases of facial spasm, especially those of middle life, belong to the so-called cryptogenic group. I have seen many a patient in whom it was impossible to detect, or even suspect, any cause of the facial spasm: local or distant; internal, neurologic or psychiatric—and this even after year-long observation, including hospital observation, during which all pertinent clinical and laboratory studies had been applied. The monosymptomatic spasm usually persists unabated, despite every conceivable treatment. This course of facial spasm led many to abandon the unsatisfactory theory of peripheral reflexive irritation and to turn to that of central, nuclear origin. One may go a step further and assume that in the so-called cryptogenic group some autochthonous degenerative process takes place in the facial nuclear or supranuclear mechanism, a process akin to that seen in paralysis agitans, torticollis and narcolepsy. Hemilateral or bilateral facial spasm is then, so to speak, a torticollis of the facial muscles. Such degeneration would release lower mechanisms, which remain intact. The unrestricted, uninhibited activity of these healthy lower mechanisms documents itself in spastic contractions of the facial muscles.

It is interesting to note the opinion of Babinski [26] (1905) on what he called "peripheral facial hemispasm." He emphasized that such a spasm does not occur with cortical lesions and incriminated a lesion

134. Wilson,[123] p. 1647.

of the facial nucleus. The same view is held here, the spasm, however, being regarded not as the result of a direct irritation but as a release phenomenon. The term "peripheral" used by Babinski to distinguish this spasm from that of cortical origin is misleading, and Bloch,[135] reviewing Babinski's article, rightly criticized it. In the latest publication on facial spasm, Ehni and Woltman [136] expressed the view that the lesion lies in the nucleus of the facial nerve or in the proximal portion of the facial nerve.

CONCLUSIONS

The primary purpose of this study is a critical analysis of the commonly accepted hypothesis that associated movements in the third nerve are due to a misdirection of regenerating fibers. An attempt has been made to show that if these associated movements are regarded as a release phenomenon due to a central lesion all the pertinent clinical facts can be more readily understood.

Of the manifold complex problems encountered during this study, only some of the associated movements among the external muscles of the third nerve have been discussed here. A discussion of the associated movements of the pupil and of those between oculomotor and other muscles has been omitted. One reason for this omission was that associated movements among the extrinsic muscles of the third nerve seem to be the cardinal symptom which offers a clue to the pathophysiologic understanding of the whole problem. Another reason was that I did not feel competent to delve deeper into the complex and perplexing problem of the physiology of ocular movements, the study of which is, nowadays, a science in itself. The famous ophthalmologist Bielschowsky devoted decades of his life to the problems of the motility of the eye. The weak point of the present study is the fact that it is written by a neurologist who is, ophthalmologically speaking, a layman. On the other hand, it may have been advantageous to have approached the problem from a neurologic angle, to have placed the emphasis on its physiologic aspect and to have coordinated the associated movements occurring with third nerve palsy with other neurologic manifestations, outside the neuro-ophthalmologic field.

This study is not intended to solve completely the problem of associated movements or to explain every symptom ever described in every case of such phenomena. It attempts only to hint at a possible new approach to the problem, and there is no intention of proving or disproving conclusively either of the hypotheses discussed. The question is only which hypothesis lends itself more readily and with greater

135. Bloch, E., in review of Babinski,[26] Neurol. Centralbl. **25**:563, 1906.

136. Ehni, G., and Woltman, H. W.: Hemifacial Spasm: Review of One Hundred and Six Cases, Arch. Neurol. & Psychiat. **53**:205 (March) 1945.

facility, with more justice to the facts, to a logical interpretation of the clinical observations, and which hypothesis is in closer accord with general neurophysiologic concepts. The hypothesis of release phenomenon propounded here, though it may appear somewhat hazardous, seems to be a workable, expandable one, capable of providing further supporting argumentation. It deserves to be used as a point of departure for future clinical, pathologic and physiologic investigations. Charles Darwin once said: "Without hypothesis, there can be no useful observation."

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TOXIC PSYCHOSES ASSOCIATED WITH ADMINISTRATION OF QUINACRINE

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EVER since quinacrine hydrochloride was introduced into the therapy of malaria, it has been considered a most valuable addition to the series of antimalarial drugs, owing to its well established effectiveness, together with its relatively low toxicity. This evaluation of the drug has not changed, even though reports of toxic effects after therapeutic doses and, in particular, of mental disorders following treatment with the drug were described as early as 1933. In that year Conoley [1] gave an unpublished report on psychosis following treatment with quinacrine. In 1934 Kingsbury,[2] utilizing observations of his own, as well as of others (Cameron,[3] Green,[4] Hoops,[5] McSwan,[6] Quaife[7]), collected a series of 12 cases of psychoses associated with quinacrine therapy, with the records available, which had been observed in the Malay States. Six more cases were published by Banerjee [8] in 1936, from India. Decherd,[9] in 1937, saw 1 case of toxic delirium with fatal outcome. He made reference to another case, observed by Chopra and Abdul Wahed.[10] In

From Gorgas Hospital, Ancon, Canal Zone.

1. Conoley, O. F., cited by Kingsbury.[2]

2. Kingsbury, A. N.: Psychoses in Cases of Malaria Following the Exhibition of Atebrin, Lancet **2**:979 (Nov. 3) 1934.

3. Cameron, I. G., in discussion on Green.[4a]

4. Green, R.: (*a*) Toxic Effects Associated with the Use of Atebrin, Malayan M. J. **9**:22 (March) 1934; (*b*) Lectures on the Development and Use of the Synthetic Antimalarial Drugs, Bull. Inst. M. Research, Federated Malay States, 1934, no. 2, pp. 1-50.

5. Hoops, A. L., in discussion on Green.[4a]

6. McSwan, D. M., cited by Kingsbury.[2]

7. Quaife, W. T., in discussion on Green.[4a]

8. Banerjee, K.: (*a*) Some Unnatural Phenomena in the Course of Atebrin Treatment, Calcutta M. J. **30**:515 (March) 1936; (*b*) Two Cases of Poisoning After Injection of Atebrin Mussonate, ibid. **31**:41 (July) 1936.

9. Decherd, G. M., Jr.: A Fatality After Atebrin-Plasmochin Treatment of Malaria, J. Trop. Med. **40**:90 (April 15) 1937.

10. Chopra, R. N., and Abdul Wahed, A. K. M.: Toxic Effects Produced by Combined Treatment with Atebrin and Plasmochin, Indian M. Gaz. **69**:213 (April) 1934.

the same year Allen, Allen and Fulghum [11] published a series of 9 cases. In 1938 another observation was reported by Bispham.[12] The same author,[13] in 1941, surveyed the literature up to that date and mentioned 7 more cases reported by Udalagama [14] from Ceylon in 1935. This paper is inaccessible to us. Other case reports equally inaccessible were cited by Choremis and Spiliopoulos [15]: 1 each of Kang and Jarvis,[16] from China (1936), and Govindaswami,[17] from India (1936). Briercliffe [18] (1935) saw psychotic disturbances during the great epidemic of malaria in Ceylon. In 1941 Lerro [19] published a case of quinacrine psychosis observed in Panama, and Wilkinson [20] described 3 cases.

While it is not at all certain that all the observations mentioned may rightly be labeled cases of quinacrine psychosis, and while, on the other hand, single case reports scattered through the huge literature on malaria may have escaped our attention, it is probably justified to consider the figure of 43 cases of quinacrine psychoses observed hitherto—the sum total of the aforementioned reported cases—as a rough estimate of the total incidence of such cases in the literature. In view of the comparative rarity of the condition, it appears worth while to publish a series of 19 cases of quinacrine psychosis which have been observed during the last eight years—1935 to 1943—ever since quinacrine therapy was instituted in Gorgas Hospital. Our series of cases is summarized in the table accompanying this article.

The neurologic after-effects of treatment with quinacrine are still less frequent than the psychoses. They seem to occur particularly in small children and consist in acute forms of polyneuritis or myeloradiculo-

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11. Allen, E. W.; Allen, H. D., Jr., and Fulghum, C. B.: Psychosis Following the Administration of Atabrine for Malaria, J. M. A. Georgia **26**:62 (Feb.) 1937.

12. Bispham, W. N.: Final Report on the Use of Atabrine in the Prophylaxis and Treatment of Malaria, Am. J. Trop. Med. **18**:545 (Sept.) 1938.

13. Bispham, W. N.: Toxic Reactions Following the Use of Atabrine in Malaria, Am. J. Trop. Med. **21**:455 (May) 1941.

14. Udalagama, L.: Mental Derangement in Malaria Cases Treated with Atebrin-Mussonate Injections, Indian M. Gaz. **70**:679 (Dec.) 1935.

15. Choremis, K., and Spiliopoulos, G.: Paralytische Erscheinungen nach Gebrauch von synthetischen Antimalaria-Mitteln, Deutsche med. Wchnschr. **64**: 1680 (Nov. 18) 1938.

16. Kang, T., and Jarvis, B. W.: Maniacal Symptoms Following the Use of Atebrin, Chinese M. J. **50**:976 (July) 1936.

17. Govindaswami, M. V.: Atebrin Poisoning, Lancet **1**:56 (Jan. 4) 1936.

18. Briercliffe, R.: The Ceylon Malaria Epidemic, 1934-35: Report by the Director of Medical and Sanitary Services, Colombo, Ceylon Government Press, September 1935.

19. Lerro, S. J.: Report of Two Cases of Toxicity to Atabrine, Mil. Surgeon **89**:668 (Oct.) 1941.

20. Wilkinson, P. B.: Mental Disturbance After the Exhibition of Atebrin, Caduceus **18**:267 (Nov.) 1939.

neuritis. Two cases have been reported in the Italian literature (Moschini,[21] 1935, and Valentini,[22] 1937) and a series of 5 cases in the German literature (Choremis and Spiliopoulos,[15] 1938). The latter observers referred to Castellani and Chalmers,[23] who observed similar neurologic pictures in patients with chronic malaria who were cured by treatment with quinine. In view of the fact that all the reported cases of polyneuritis in children occurred with chronic malaria, the etiologic part played by quinacrine cannot very well be estimated.

With regard to observations on adults, case 2 reported by Lerro [19] deserves to be mentioned; in this case treatment with quinacrine was followed by paresthesias over the entire body, associated with nausea, vomiting and a choking sensation. In view of the fact that in animal experiments quinacrine in toxic doses causes clonic convulsions (Molitor [24]), the occurrence of epileptiform fits after treatment with the drug mentioned by Stitt [25] (in cases of Field and Niven,[26] Vardy [27] and van Heukelom and Overbeek [28]) is of interest.

INCIDENCE

The total number of cases in Gorgas Hospital in which quinacrine treatment was employed during the period from May 1935 to November 1943 was 4,876, of which 2,653 were cases of tertian malaria and 2,223 cases of estivoautumnal malaria. The few cases of mixed infection have not been counted separately but are included in these figures. Quinacrine hydrochloride was usually given in conjunction with quinine or pamaquine naphthoate. However, quinacrine was, in these cases, the

21. Moschini, S.: Polineurite cerebrospinale acuta motoria, di natura tossica, ad inizio apoplettiforme in una bambina di due anni, Riv. di clin. pediat. **33**:823 (July) 1935.

22. Valentini, P.: A proposito di una grave sindrome mielo-radicolo-neuritica insorta nel corso di terapia atebrinica, Pediatria **45**:51 (Jan.) 1937.

23. Castellani, A., and Chalmers, A. J.: Manual of Tropical Medicine, ed. 3, London, Baillière, Tindall & Cox, 1919, pp. 1175-1176.

24. Molitor, H.: Antimalarials Other than Quinine, in Moulton, F. R.: A Symposium on Human Malaria with Special Reference to North America and the Caribbean Region, Publication 15, American Association for the Advancement of Science, 1941.

25. Strong, R. P.: Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases, ed. 6, Philadelphia, The Blakiston Company, 1942.

26. Field, J. W., and Niven, J. C.: Clinical Comparison of Atebrin Mussonate with Quinine Bihydrochloride, Tr. Roy. Soc. Trop. Med. & Hyg. **29**:647 (April 8) 1936.

27. Vardy, E. C.: Notes on a Clinical Investigation of the Treatment of Malaria by Atebrin Mussonate Injections, Malayan M. J. **10**:67 (Sept.) 1935.

28. van Heukelom, A. S., and Overbeek, J. G.: The Treatment of Acute Malaria with Atebrin Injections, Geneesk. tijdschr. v. Nederl.-Indië **76**:2507 (Oct.) 1936.

principal antimalarial drug, and quinine and pamaquine naphthoate were used in follow-up treatment. The average dose of quinacrine hydrochloride used was 1.7 to 1.8 Gm., given over the course of five to six days, and only in a negligible number of cases did it exceed 2.1 Gm.

We observed 19 cases of quinacrine psychosis. The incidence, therefore, was 0.39 per cent, or about 1 out of 250 cases. In order to calculate the incidence for estivoautumnal and tertian malaria separately, we have to eliminate 6 of our 19 cases, because in 3 of them the type of parasite was unknown, in 2 cases there was mixed estivoautumnal and tertian infection and 1 was a case of quartan malaria. For the proportionately reduced total number of cases of estivoautumnal and tertian malaria treated with quinacrine, the incidence of psychosis for the two types of malaria was 0.46 and 0.33 per cent, respectively, and therefore somewhat higher for estivoautumnal than for tertian malaria.

The incidence as given in the literature varies considerably.

Kingsbury [2]	12 "among several thousand"
Bispham [12]	1 in 422 cases
Green [4]	2 in 750 cases
Allen Jr.[29]	1 in 2,000 cases (estimate)
Udalagama [14]	7 in 644 cases

The only exact figures are those of Bispham,[12] Green [4] and Udalagama.[14] The high incidence found by the last author is explained by two facts: (1) He used intramuscular injections of quinacrine mussonate, a method which seems to be more toxic than the usual oral administration of quinacrine hydrochloride; (2) his observations also include states of depression following treatment with quinacrine, and it is doubtful whether these can be counted as true quinacrine psychoses. The figures of Bispham [12] and Green [4] would be equivalent to 0.24 and 0.27 per cent, respectively, values considerably lower than ours. However, their material (1 and 2 cases, respectively) is obviously too small for comparison.

SYMPTOMS

To illustrate the clinical picture of quinacrine psychosis, a typical case will be reported in brief.

CASE 13.—A white American, a man aged 36, was admitted to Gorgas Hospital on Nov. 5, 1942, with mixed tertian and estivoautumnal malaria. He was placed under quinacrine therapy and given 0.2 Gm. of the drug intramuscularly, followed by oral administration of 0.1 Gm. three times a day. On the night of November 12, after an intake of 2 Gm. of quinacrine hydrochloride within six days, he suddenly became confused, irrational and resistive and would not stay in bed. He still had fever on that day; however, the last time that the parasites of estivoautumnal and tertian malaria had been found in his blood was five and four days, respectively, prior to the outbreak of his psychosis. The following morning he became noisy, excited and talkative and began throwing bedside articles about the ward. It became necessary to put him in a seclusion room.

29. Allen, H. D., Jr., in discussion on Allen, Allen and Fulghum.[11]

Quinacrine therapy was immediately discontinued, and he was placed under treatment with quinine, increased intake of fluid and high doses of vitamin B complex, including parenteral injections of thiamine hydrochloride. He soon quieted down, and on November 14 he was mentally clear, rational and oriented.

This patient exhibited, immediately after an attack of mixed tertian and estivoautumnal malaria, and at the end of a course of a total 2 Gm. of quinacrine hydrochloride, an acute psychosis, with all the characteristics of an organic reaction type: confusion, restlessness, pronounced psychomotor excitement, destructiveness, increased pressure of speech and clouded sensorium. The psychosis subsided almost as suddenly as it had developed, after little more than one day's duration.

In most of our cases (e. g., cases 2, 3, 10 and 12), essentially the same psychopathologic picture, with minor variations, was exhibited. Usually the emotional factor seems to be predominant, producing the syndrome of confused mania or that of anxiety psychosis or panic; in other cases, catatonic features are noticeable (cases 1, 5, 6 and 15); again, there are cases with prominent paranoid content (cases 7, 9 and 14); visual and auditory hallucinations may dominate the picture (cases 9, 11 and 16), and, finally, a full blown toxic delirium may be present (cases 4 and 15).

There is nothing specific in the psychiatric symptoms of the quinacrine psychosis. It corresponds to the well known type of toxic psychosis of various causes, most frequently seen subsequent to endotoxic processes, such as hyperthyroidism, or nutritional deficiency, such as pellagra or other forms of B avitaminosis. Neurologic examination almost invariably revealed nothing abnormal, which goes to prove that the condition is not due to any localized pathologic process of encephalitic character. The variations mentioned—manic, catatonic, paranoid and hallucinatory—are most likely due to differences in the prepsychotic personality structure.

Unusual clinical features develop in cases in which quinacrine psychosis is superimposed on some organic pathologic process in the brain. This occurred in 2 cases in our series, which therefore deserve to be reported separately.

Case 8.—A white American man aged 22 was transferred on July 10, 1942 to Gorgas Hospital from an outlying hospital, where he had been under treatment for malaria since May 30, 1942. On May 31, 1942 his blood smear revealed parasites of estivoautumnal malaria. He was placed on routine quinine therapy, followed by a course of quinacrine treatment. The total dose of the drug could not be ascertained. On July 6, 1942 a blood smear was found positive for trophozoites of tertian malaria. Again, he was placed on quinacrine therapy, the dose being unknown. At that time he began to exhibit mental symptoms, manifested by vague and irrelevant conversation, bewilderment and confusion. Because of his mental condition, he was transferred to Gorgas Hospital. At that time, his tem-

perature was normal and his blood negative for malaria organisms. He was confused, disoriented, perplexed, mentally retarded and hesitant in speech and showed impairment of recent memory. The sensorium was clouded. The skin and scleras were lemon yellow. Neurologic examination revealed nothing abnormal. Under treatment with forced intake of fluids, large amounts of vitamin B complex and parenteral injection of thiamine hydrochloride, he began to show improvement. On July 24, 1942 his mental state appeared entirely clear. After the psychosis had subsided, however, he was noted to be slow in grasping ideas and seemed intellectually retarded. His past personal history revealed that he had always been slow to learn, had to be shown repeatedly how to perform certain duties and was mentally below average. His mentality was estimated to be that of a medium grade moron. He was discharged from the hospital on August 2 as recovered from malaria and the toxic psychosis.

While the history in this case left hardly any doubt that quinacrine was the main causative factor, the psychiatric picture differed considerably from the usual pattern. Instead of the hyperactivity and psychomotor excitation usually seen, the patient appeared retarded and bewildered and exhibited impairment of recent memory. His psychosis lacked productivity, hallucinations, delusions, and pathologic impulses being entirely absent. Another relevant fact distinguishing this case from most of our series is that though quinacrine therapy was immediately discontinued and the routine vitamin treatment given it took eighteen days for the psychosis to clear up. The theory that the atypical picture and course of the toxic psychosis in this case were due to its being superimposed on an organic cerebral defectiveness is, though not conclusive, highly suggestive. It appears to be just a special case in kind of the prepsychotic personality modeling and modifying the structure of a psychosis, except that with mental deficiency the preexisting personality is so basically different from the average that, as a result of the toxic process going on in an already abnormal brain, an altogether atypical picture develops.

Case 6.—A Salvadorian man aged 39 was admitted to Gorgas Hospital on July 5, 1942, with a temperature of 102 F. and a blood smear positive for the parasites of estivoautumnal malaria. He was placed on quinacrine therapy, receiving 0.6 Gm. daily for four days, or a total of 2.4 Gm. On the second day of hospitalization his temperature dropped to normal. The last blood smear which was positive for parasites of estivoautumnal malaria was taken on July 6. During the night of July 9 he suddenly became disturbed, yelling, screaming and thrashing about in his bed. Seclusion and sedation were necessary. Next morning he still was acutely excited, disturbed, hyperactive and catatonic. He would assume a prayerful attitude for one minute and the next minute go through numerous bizarre mannerisms. All tendon reflexes were exaggerated. The patient was placed on a regimen of high fluid intake, sedation, parenteral administration of thiamine hydrochloride and oral use of vitamin B complex. On July 8 the Wassermann reaction of the blood was negative, and the Kahn reaction was a doubtful 1 plus. Examination of the spinal fluid, on July 14, revealed a 2 plus Wassermann reaction, 1 plus reactions in the ammonium sulfate and phenol tests and a colloidal

gold curve of 5555421100. The cell count was 0. During the following weeks, the patient had a temperature ranging from 100 to 104 F. He remained in a state of delirium, talking or muttering incessantly, was hyperactive, excited and resistive and had to be kept in restraint in spite of sedation with paraldehyde and sodium amytal. Examinations of the blood, when repeated, showed the same reactions. After the Wassermann reaction of the spinal fluid had been reported as 2 plus, treatment was started with graduated doses of potassium iodide and bismuth subsalicylate in oil, 0.13 Gm. given intramuscularly once a week. The patient's mental condition showed no improvement, and the course was progressively downhill. He died on August 10, with a terminal temperature of 108 F.

Autopsy (significant observations only).—The body was that of a moderately emaciated, asthenic, brown Salvadorian. The left pupil measured 0.7 cm. and the right 0.5 cm. The lips were pale and cyanotic. The gums had a blue color around the base of the teeth. The mucous membrane of the mouth was pale. Small, "shotty" lymph nodes were palpable in the axillary and inguinal regions. Scattered over the back, shoulders and neck was a fine papular eruption. There was a small decubital ulcer over the tip of the sacrum. The nails appeared faintly cyanotic. The dura appeared slightly thickened but could be stripped from the skull without great difficulty. Cerebrospinal fluid withdrawn by cisternal puncture was clear and yellow. The meninges over the entire cerebrum appeared thickened. Particularly along the midline this thickening assumed the form of numerous fine granulations, resembling pacchionian granules but somewhat more diffuse. The sulci were slightly widened, and the meninges filling the sulci appeared to have small patches of scarring, averaging 0.3 cm. in diameter. The blood vessels of the meninges appeared grossly dilated.

The brain was relatively firm and retained its contour well in sectioning. Its weight was 1,330 Gm. The vessels within the parenchyma of the brain stood out prominently, as though moderately congested. The ependyma of the lateral and fourth ventricles showed minimal roughening but no granulation.

The lymphoid follicles at the base of the tongue were moderately enlarged. The larynx, trachea and bronchi were filled with frothy, white, slightly blood-tinged serous fluid. The mucous membrane of the lower part of the trachea and the bronchi was greatly congested. Approximately 15 cc. of fluid lay within the left pleural cavity. The right pleural cavity was completely obliterated by firm fibrous adhesions, binding all faces of the lung to the parietal pleura. The upper lobe of the left lung was pale pink, soft and crepitant. The lower lobe of the left lung was firm and reddish purple with areas of bluish discoloration. On section the upper lobe appeared light red. The lower lobe was dark red, and serosanguineous fluid could be expressed from the bronchioles. The right lung was relatively firm but slightly crepitant. On section the lung appeared dark red, and serosanguineous fluid could be expressed from its bronchioles. The heart muscle was dark brown and felt somewhat flabby. The aortic valve had a small plaque of calcification in the right cusp. The ascending portion, the arch and the proximal portion of the descending part of the thoracic aorta showed pronounced thickening and wrinkling, forming deep longitudinal corrugations. Little sclerosis was present. Most of these corrugations appeared to be due to fibrous scarring. This condition was most pronounced in the ascending portion of the aorta, where there was an area of apparent dilatation, starting 2 cm. from the aortic valve. These corrugations extended to the ostiums of the coronary arteries but not into these vessels themselves. The liver appeared somewhat enlarged and weighed 1,780 Gm. The surface and the cut sections were reddish brown; scattered through them were numerous small areas of light yellow, measuring approximately 0.5 cm. in diameter

Data on Nineteen Cases of Quinacrine Psychoses Occurring at Gorgas Hospital from 1935 to 1943

Case: Sex; Age	Race	Type of Malaria *	Dose of Quinacrine at Start of Psychosis, Gm.	Days Elapsed Between Start of Psychosis and: Last Fever	Last Positive Smear	Last Dose of Quinacrine	Duration of Psychosis, Days	Symptoms	Treatment	Outcome and Comments
1 F 45	Foreign white	E. A.	1.5	2	0	0	32	Patient noisy, disturbed, restless, confused, removing clothes; later filthy, smearing feces, resistive, unmanageable	Sedation	Recovery. Quinacrine had been continued for one week after outbreak of psychosis, up to total dosage of 3.6 Gm.
2 F 45	Negro	E. A.	1.8	2	2	1	4	Patient noisy, screaming, crying, talking incoherently, throwing objects around, confused	Sedation, quinine, ovarian tablets	Recovery
3 M 30	White American	F. U. O.	1.9	1	Smear always negative	0	1½	Patient irrational, noisy, crying, surly, mumbling incoherently to himself, confused, restless, emotional	Sedation	Recovery
4 M 26	Foreign white	Tertian	3.0	10	8	2	13	Toxic delirium; patient hyperactive, excited, muttering	Sedation, quinine, fluids, vitamin B	Death. Lemon yellow skin; albuminuria, casts, leukocytes 9,000-20,000; cultures of spinal fluid and blood sterile
5 M 19	Foreign white	E. A.	1.8	0	2	0	2	Patient confused, uncooperative, catatonic, clouded sensorium	Fluids, vitamin B, sedation	Recovery
6 M 39	Foreign white	E. A.	2.4	3	3	0	31	Patient disturbed, screaming, excited, hyperactive, catatonic, bizarre mannerism, delirious; temperature up to 108 F	Antisyphilitic treatment, vitamin B	Death. Autopsy; diagnosis, dementia paralytica
7 M 31	White American	Quartan	Unknown	Unknown	Unknown	Unknown	3	Patient confused, disoriented paranoid; visual hallucinations	Quinine, sedation, vitamin B	Recovery. Yellow-tinged skin
8 M 22	White American	E. A., tertian	Unknown	Unknown	1-2 days for tertian	0	18	Vague, irrelevent talk; patient bewildered, confused, uncooperative, retarded; clouded sensorium; impairment of recent memory	Vitamin B	Recovery. Yellow skin; medium grade moron

9 M 31	Foreign white	Tertian	1.8	3	4	0	2	Patient excited, suspicious; auditory and visual hallucinations; apprehensive, paranoid; depressive delusions	Vitamin B, sedation, quinine	Recovery
10 M 28	White American	Unknown	5.7	Unknown	Unknown	1	2½	Patient violent, confused, excited, apprehensive, destructive; mumbling, incoherent speech; bilateral ankle clonus	Saline and dextrose solution, sedation, vitamin B	Recovery. Lemon yellow skin
11 M 22	White American	Tertian	2.2 (0.2 i.m.)	2	0	3	1	Patient excited, violent; auditory and visual hallucinations; delusions of grandeur	Sedation, vitamin B	Recovery. Tertian parasites in blood until 11th day
12 M 24	Foreign white	F. U. O.	1.6	1	Always negative	0	2	Patient apprehensive, talking incessantly, violent, confused	Sedation, vitamin B	Recovery
13 M 36	White American	Tertian, E. A.	2.0 (0.2 i.m.)	0	4	0	1	Patient confused, irrational, resistive, noisy, excited, talkative, throwing objects around	Sedation, dextrose saline solution, vitamin B	Recovery
14 M 33	White American	Tertian	1.1	0	0	0	1	Patient confused, disoriented, irrational, delusional	Quinine, dextrose, sedation	Recovery
15 M 16	Negro	Tertian	1.7	6	5	0	6	Patient wild, violent, noisy, disoriented; auditory hallucinations; clouded sensorium; temperature 100 F.	Sedation, vitamin B	Recovery. Psychosis lasted 6 days, cleared up 1 day after vitamin B therapy was started
16 M 28	White American	E. A.	0.9	0	0	0	7	Patient confused, bewildered, disoriented; auditory hallucinations; clouded sensorium; temperature 100 F.	Sedation, dextrose saline solution, vitamin B	Recovery. Scleras yellow; psychosis, lasting 5 days, cleared up 1-2 days after vitamin B therapy was started
17 M 23	White American	E. A.	1.5	5	Unknown	5	20	Patient confused, hyperactive; loss of recent memory; loss of inhibitions	Vitamin B, sedation	Recovery
18 M 25	Foreign white	E. A.	0.5 (0.2 i.v.)	0	0	0	½	Manic excitement; patient confused, hyperactive	Sedation	Recovery. Psychosis started 1½ hours after intravenous administration of 0.2 Gm. quinacrine hydrochloride
19 M 29	Foreign white	Tertian	1.9	Unknown	Unknown	0	14	Patient very talkative, noisy, emotionally unstable	Vitamin B, sedation	Recovery

* E. A. indicates estivoautumnal malaria; F. U. O., fever, undetermined origin.

and resembling focal fatty degeneration. The spleen measured 14 by 7 by 3 cm. and weighed 165 Gm. The capsule appeared thickened. The trabecular markings were unusually prominent. The smooth surface of the kidneys showed scattered dark brown, depressed areas. The pelves appeared slightly thickened and congested and contained purulent material. In the esophagus there were two areas of ulceration, measuring 3 by 1 and 1.5 by 0.5 cm., respectively. These ulcerations were apparently produced by an in-dwelling stomach tube, which was needed to feed the patient. The gastric mucosa showed a few scattered petechial hemorrhages. Moderate congestion and apparent petechial hemorrhages were present in the sigmoid and rectum. A single female ascarid was found in the colon.

Microscopic Examination of the Brain.—The leptomeninges were composed of fairly heavy strands of connective tissue, with moderate lymphocytic infiltration. The vessels of the meninges were engorged with blood. In the ganglion cells of the frontal cortex the Nissl substance was lacking. A moderate amount of fine, yellow granular material, resembling lipid pigment, was present within the cytoplasmic portion of the cells. A few of the blood vessels appeared to have undergone disruption and extravasation of red cells into the nerve tissue. There was slight lymphocytic infiltration in the Virchow-Robin spaces. The ependyma of the fourth ventricle was made up of a regular layer of small cells with occasional small patches of subependymal glial proliferation.

Anatomic Diagnosis.—The diagnosis was syphilitic meningoencephalitis, a few focal hemorrhages of the cerebral cortex, bronchopneumonia and syphilitic and arteriosclerotic aortitis.

In this case a toxic psychosis developed after a course of 2.4 Gm. of quinacrine hydrochloride, superimposed on undiagnosed dementia paralytica. As can be seen from the autopsy report, the process of syphilitic meningoencephalitis appears to have been in a rather early stage and not very active, as was also demonstrated by an only doubtfully positive Kahn reaction of the blood and the absence of cells in the spinal fluid. Nevertheless, the disease seems to have been sufficiently advanced to produce, in combination with the toxic effect of quinacrine, a severe, fatal delirium, of thirty-two days' duration. While it is true that fulminant dementia paralytica may occasionally show rapid progression toward death, the clinicopathologic and autopsy observations in our case would hardly be consistent with such a course. On the other hand, it is known that quinacrine psychosis is usually benign and of short duration. It appears, therefore, justified to attribute the peculiar clinical picture and fatal outcome in this case to the deleterious effect of quinacrine on a brain which was already diseased with early dementia paralytica.

The symptoms of quinacrine psychosis, as described in the literature, essentially agree with our observations. States of manic or hypomanic excitement seem to be most frequent (Kang and Jarvis[16]; Bispham[12]; Allen, Allen and Fulghum.[11]) Probably those cases labeled instances of "cerebral excitation" by early observers (Conoley,[1] Hoops,[5] McSwan,[6] Green[4]) belong in the same category. The occurrence of delirium has been reported by Govindaswami,[17] Decherd[9] and Lerro.[19] In a case reported by Kingsbury[2] visual hallucinations were prevalent in an

otherwise catatonic condition. A schizophrenia-like psychosis was observed by Banerjee[8b]; a paranoid syndrome, by the latter and by Cameron.[3] In cases of Allen, Allen and Fulghum[11] and of Kingsbury[2] confusional states were present. We did not observe depressive conditions, such as were described by Kingsbury,[2] Banerjee,[8a] Bispham[12] and Quaife.[7] We did not see, either, cases of prolonged coma, as mentioned by Beckman.[30]

ONSET, COURSE, DURATION AND OUTCOME

Quinacrine psychoses start usually, though not always, after the fever caused by malaria has subsided and no more parasites are found in the blood. As can be seen in our table, the time intervals between the last day of fever and the onset of the psychosis were, in those cases in which exact data were available, as follows:

No. of Days	No. of Cases
0	5
1	2
2	3
3	2
5	1
6	1
10	1

The average interval was 2.2 days; the median, 2 days. The time intervals between the last positive blood smear and the onset of the psychosis were distributed as follows:

No. of Days	No. of Cases
0	4
1	1
2	3
3	1
4	2
5	2
8	1

The average interval was 2.6 days; the median, 2 days. As to the relationship between the termination of administration of quinacrine and the onset of the psychosis, in most of our cases quinacrine was discontinued only when psychotic symptoms occurred (in 12 out of 17 cases in which data were available). Usually it was the same day on which the course of quinacrine therapy had been, or was to be, terminated anyway. However, there were 2 cases in which one day elapsed between the last dose of quinacrine and the onset of the psychosis and 3 cases in which the

30. Beckman, H.: Treatment in General Practice, ed. 4, Philadelphia, W. B. Saunders Company, 1942, p. 97.

intervals were two, three and five days, respectively. In 1 case—the first in our series, observed at a time when quinacrine as a possible cause of mental disorder was not yet considered by the observers in Gorgas Hospital—treatment with the drug was continued after the outbreak of the psychosis, up to a total dose of 3.6 Gm. The psychosis lasted thirty-two days.

The onset is usually sudden, but it may be gradual, preceded by a short period—one day or less—of nervousness, malaise, restlessness or insomnia. The psychosis develops, in most cases, to a climax within one day or less, remains at its height for a variable length of time and is followed by rapid recovery. Its duration in our series was as follows:

Duration, Days	No. of Cases
1 or less	3
1½	2
2	3
2½	1
3	1
4	1
6	1
7	1
13*	1
14	1
18	1
20	1
31*	1
32†	1

* Fatal outcome.

† In this case, quinacrine therapy had been continued for another week after the psychosis had started.

The average duration of the psychosis in those cases in which the outcome was recovery was 8.5 days; the median duration, 2.5 days.

The outcome of quinacrine psychosis is almost invariably complete recovery. However, in addition to the fatal case of quinacrine psychosis with dementia paralytica, just reported, we observed another fatal case which deserves to be reported in some detail.

CASE 4.—A Puerto Rican man aged 26 was admitted to Gorgas Hospital on Feb. 25, 1943, as a transfer from an outlying hospital. He had been admitted to the latter on February 5, with a temperature of 99.2 F. and a history of chills, fever, headache and profuse sweating, of one day's duration. On February 6 the smear was positive for trophozoites of tertian malaria. He received an initial dose of 3 Gm. of quinine sulfate, followed by 0.66 Gm. three times a day for five days; then quinacrine hydrochloride, 0.1 Gm. three times a day for ten days (a total of 3 Gm.); then quinine sulfate, 0.66 Gm., three times a day for five days. The course of his illness

was afebrile after the first day and was uneventful except for a furuncle in the right axilla, which was incised and drained on February 13. A smear on February 18 was negative for malarial organisms. The patient was to be discharged on February 25, when it was noticed that his behavior was peculiar. It was learned from the chaplain that he had noted some mental aberration a few days previously, or about two days after the completion of the course of quinacrine therapy. On admission to Gorgas Hospital, the patient's temperature was 101.6 F. The blood count was 70 per cent hemoglobin, 3,950,000 red cells and 11,400 white cells, with a differential count of 72 per cent neutrophils and 28 per cent lymphocytes. The general physical examination revealed nothing significant except for lemon yellow discoloration of the skin and scleras. Mentally the patient exhibited the picture of toxic delirium, with marked hyperactivity, excitement and constant muttering. He had to be controlled with sedatives. On February 27 his temperature rose to 104.8 F., and, although all smears were negative for the parasites, it was considered advisable to place him under treatment with quinine sulfate. Treatment with forced intake of fluids, high doses of vitamin B* complex and thiamine hydrochloride had already been given. Examination of the spinal fluid on February 27 revealed 5 lymphocytes per cubic centimeter, 0.02 Gm. of protein per hundred cubic centimeters, negative serologic reactions and a normal colloidal gold curve. The temperature rose to 106.6 F. (rectally). A roentgenogram of the chest, taken on March 1, revealed a small patch of pneumonitis in the middle portion of the right lung. He was placed under treatment with sulfadiazine, with an initial dose of 6 Gm. and a maintenance dose of 1.0 Gm. every four hours. Examination of the spinal fluid on March 1 showed 5 lymphocytes per cubic millimeter, 119 mg. of glucose per hundred cubic centimeters, 800 mg. of sodium chloride and 0.031 Gm. of protein per hundred cubic centimeters, negative serologic reactions, a normal colloidal gold curve and sterile cultures. Repeated blood cultures were sterile; the albumin-globulin ratio, fasting blood chemistry and icteric index were normal, and agglutination tests for typhoid, paratyphoid and brucellosis were negative. Repeated specimens of urine showed a trace to a 2 plus reaction for albumin, a few pus cells, occasional red cells and granular and hyaline casts. Examination revealed no tyrosine crystals. The white blood cell count ranged from 9,200 to 20,000 and the differential count, from 78 neutrophils, 5 eosinophils and 17 lymphocytes to 57 neutrophils, 3 myelocytes 1 eosinophil and 37 lymphocytes, per hundred cells. On March 2 the patient showed temporary improvement, which continued until March 3, when his temperature rose to 103 F., and he again became noisy, restless and disturbed. From this day his course was progressively downhill, until he died on March 7.

Autopsy (March 7; significant observations only).—The brain weighed 1,350 Gm. The leptomeninges and parenchyma were slightly congested. Lymphoid follicles at the base of the tongue were prominent. The heart was slightly larger than usual. The liver was distinctly enlarged, weighing 2,500 Gm. The parenchyma was firm, dark red and bloody and appeared somewhat swollen, tending to bulge above the cut surface. The spleen was enlarged, weighing 370 Gm. The parenchyma was firm, dark red and rubbery. On the cut surface of the kidneys there could be seen within the cortices barely visible glomeruli, which stood out as tiny shiny spots. Within the jejunum there were found 4 worms of the species N. americanus.

Microscopic Examination.—Brain: A small amount of granular, eosinophilic material was present in the subarachnoid space. The nuclei of the nerve cells were possibly slightly hyperchromatic.

Liver: The venous sinuses in all portions of the lobules were distended with blood. The cytoplasmic borders were rather indistinct. The cells of Kupffer contained a moderate amount of yellowish black pigment, most of which appeared to be malaria pigment.

Spleen: The malpighian corpuscles were rather large, with prominent germinal centers. The venous sinuses were congested, and the follicles stood out prominently against this reddish background. Only a small amount of pigment was present within the spleen.

Kidneys: The glomeruli were rather large, and the loops were stuffed with blood, so that each capillary appeared swollen. The lumens of some of the tubules contained a small amount of amorphous eosinophilic material. Only a rare tubule contained an albuminous cast.

Prostate Gland: The lumen of practically every acinus was packed with pus and cellular debris. The surrounding areas of some of the acini were packed with pus, in a subacute inflammatory reaction, with infiltration by lymphocytes and polymorphonuclear leukocytes.

Anatomic Diagnoses.—The diagnosis was mild congestion of the brain and meninges; congestion of the liver with hepatomegaly; splenomegaly; infection with N. americanus; subacute purulent prostatitis; malarial pigment in the spleen and liver; congestion of the renal glomeruli, and yellowish tinge to the internal organs (quinacrine ?).

In this case there developed, two days after termination of a course of quinacrine therapy for tertian malaria, a subacute toxic delirium with febrile temperatures, and the patient died thirteen days later, with hyperpyrexia. The autopsy report is remarkable for the absence of significant observations. The brain and meninges were moderately congested. There were marked congestion of the liver, the spleen and the kidneys; subacute purulent prostatitis, and a yellowish tinge to the internal organs. These observations rule out cerebral malaria, which could hardly be considered anyhow in a case of tertian malaria. The remote possibility that death might have been due to the purulent prostatitis is ruled out by repeated sterile blood cultures and the absence of any observation at autopsy suggestive of septicemia. Hence, the cause of death was toxic delirium, most probably due to quinacrine. Still, we cannot account for the fact that the development in this case was so extremely serious except by assuming a specific hypersensitivity to quinacrine. It is of interest to note that the patient in case 10 in our series, who received the large dose of 5.7 Gm. of quinacrine hydrochloride, recovered from his psychosis after two and one-half days. These observations certainly point toward considerable individual differences in tolerance toward the drug.

Our observations agree fairly well with those of other authors. No data were available in the literature regarding the time elapsed between the last attack of fever or the last positive blood smear, and the onset of psychosis. The time elapsing between the last dose of quinacrine and the onset of psychosis varied in 17 cases observed by Kang and Jarvis,[16] Decherd,[9] Allen and co-workers,[11] Briercliffe[18]

and Kingsbury,[2] from no to eighteen days, with a median of 2 days. The duration of the psychosis in 26 cases was observed by Kang and Jarvis,[10] Banerjee,[8b] Green,[4] Allen and co-workers,[11] Bispham[12] and Kingsbury[2] from one-half to thirty-seven days. The average duration in 18 of these cases (in the rest of them the data were not given in all detail) was 4.4 days; the median, 2 days. In all the cases reported in the literature, with the exception of 1 fatal case, the outcome was complete recovery. No case of chronic psychosis following quinacrine therapy has been recorded. The 1 fatal case was described by Decherd.[9] The patient had received only 0.6 Gm. of quinacrine hydrochloride and 0.06 Gm. of pamaquine naphthoate in three days, when both drugs were discontinued and quinine was substituted, because of icterus and swelling of the liver. Two days later the patient lapsed into delirium. He became cyanotic; pulmonary edema developed, and he died on the second day of his psychosis. Autopsy was not performed. The impression prevails that in this case psychosis and death were due to acute damage to the liver. However, the clinically observed swelling of the liver may have been due, as in our own case, to congestion only, and the apparent jaundice, to deposits of dye in the skin, as it occurs frequently in patients treated with quinacrine.

ETIOLOGY AND PATHOGENESIS

That quinacrine was the direct cause of, and the most essential factor in, the psychoses in the cases observed by us and by other authors appears to be established by the following facts: 1. The psychosis developed invariably a short time after a course of quinacrine treatment had been given. 2. In almost all cases it subsided shortly after the administration of quinacrine had been discontinued, whereas it went on when the drug was still given after the mental symptoms had made their appearance (case 1). 3. The incidence of quinacrine psychosis, while rather low, is still by far higher than the incidence of toxic psychosis of unknown origin in the general population. This rules out the possibility of mere coincidence. 4. Cerebral malaria cannot be the cause of the mental disorder, (*a*) because the psychosis started in most cases after the patient had been cured of malaria and (*b*) because the incidence of the psychosis is not much lower with tertian than with estivoautumnal malaria, whereas cerebral involvement in cases of untreated tertian malaria is most uncommon. 5. While it is true that many of our patients received quinine or pamaquine naphthoate in addition to quinacrine, no toxic psychoses were observed after the use of either of these drugs without quinacrine.

Clark,[31] who was acquainted only with Kingsbury's[2] series, made the objection that the mental disorders may be due to malaria itself and raised the question whether the incidence of so-called quinacrine psychosis is not about the same as that of toxic psychosis from other causes in the general population. These objections are dealt with under items

31. Clark, H. C.: Recent Research on Prophylaxis and Treatment of Malaria, South. M. J. **29**:752 (July) 1936.

3 and 4 in the preceding paragraph. Oden [32] mentioned a patient who came to the institution with a psychosis after quinacrine therapy; the condition cleared up; he left the institution and after some time came back with the same type of psychosis, though he had not been taking the drug. Another patient, after being cured of so-called quinacrine psychosis, was given the drug again, but this time he exhibited no mental disorder. These observations would tend to make one reconsider the etiologic importance of quinacrine if they had been substantiated by exact data on doses and on time which elapsed between the two psychoses or the two courses of quinacrine treatments, respectively. Unfortunately, they were not.

Granted, therefore, that the concept of quinacrine psychosis is justified, the question arises what factors determine the toxic effect, in a small number of cases, of a drug of comparatively low toxicity. Probably, the dose is of no importance.

In our series, the total doses of quinacrine hydrochloride given up to the outbreak of the psychosis varied considerably.

Dose, Gm.	No. of Cases
0.5	1
0.9	1
1.1	1
1.5	2
1.6	1
1.7	1
1.8	3
1.9	2
2.0	1
2.2	1
2.4	1
3.0	1
5.7	1
Unknown	2

The patient in case 4, who received 3 Gm., died in delirium after thirteen days; the patient in case 10, who received 5.7 Gm., survived and recovered after two and a half days. The average dose was 1.9 Gm.; the median dose, 1.8 Gm. The doses of quinacrine hydrochloride which were followed by a psychosis varied in the cases of Kang and Jarvis,[16] Banerjee,[8b] Bispham,[12] Decherd,[9] Lerro,[19] Green,[4] Briercliffe [18] and Kingsbury [2] from 0.6 to 2.1 Gm., with an average of 1.6 Gm. in 22 cases. The League of Nations' Commission on Malaria [33] (cited by Stitt [25]) reported that pyschoses have been observed especially in cases in which

32. Oden, J. W., in discussion on Allen, Allen and Fulghum.[11]

33. Fourth General Report of the Malaria Commission, Bull. Health Organ., League of Nations **6**:895-1153, 1937.

treatment with quinacrine was prolonged or the doses were large or excessive and in cases in which quinacrine mussonate was given by injection and followed by the oral use of quinacrine hydrochloride. In some of our cases quinacrine had been given parenterally. According to Briercliffe,[18] mental symptoms would appear toward the end of a five day period of oral administration of 0.3 Gm. of quinacrine four times a day, whereas in case of intramuscular injection they would follow soon after the first injection or within twenty-four hours after the second injection. With regard to the effect of parenteral administration of quinacrine, case 18 in our series deserves to be reported.

CASE 18.—A Panamanian aged 25 was admitted to the hospital on Sept. 8, 1943, with a history of headache, chills, anorexia and nausea for seven days preceding his admission. He had never had malaria before. The temperature on his admission was 100.6 F.; otherwise physical examination showed essentially a normal condition. The blood smear was positive for estivoautumnal malaria on the day of his admission. The patient received 0.3 Gm. of quinacrine hydrochloride by mouth. On the following day his temperature rose to 104 F., and a few parasites were still found in his blood. In the morning the patient was perfectly rational and not excited. At 9 a. m. of this day he received 0.2 Gm. of quinacrine hydrochloride intravenously. At 10:30 a. m. he was found sitting in his bed, swinging his legs, rapping on the bed and conversing excitedly with other patients. Shortly afterward he became violently hyperactive, threw a water jar and a medicine capsule on the floor and talked about getting out and buying meat and champagne. When put in a wheel chair, he started throwing himself around and shouting at the top of his voice. Sedation was effected with 3 grains (0.195 Gm.) of sodium amytal and ¼ grain (1.6 mg.) of morphine sulfate and he received large doses of thiamine hydrochloride and nicotinic acid. His temperature was 105.6 F. at 4 p. m. At that time the patient was semicomatose, and obviously under the influence of sedatives. At 7:15 p. m. he was awake and talked rationally, though mentally somewhat sluggish. His temperature dropped to 101.0 F. at midnight and was normal the next day. He remained mentally clear, with normal temperature. Further smears were negative for the parasites, and the patient was discharged on Sept. 16, 1943.

In this case it appears that the sudden rise of the quinacrine level in the patient's blood produced by intravenous administration of 0.2 Gm. of the drug, in addition to 0.3 Gm. given orally the day before, was an important factor responsible for the outbreak of an acute manic state, of only a few hours' duration.

According to Allen and co-workers,[11] there seems to be a relation between the dose per kilogram of body weight and the duration of mental symptoms. All 4 of their patients who took more than 25 mg. per kilogram of body weight had symptoms of over ten days' duration, although 2 patients who had symptoms lasting more than ten days took only 19.1 and 24.1 mg. per kilogram of body weight, respectively.

These observations suggest a positive correlation between the dose of quinacrine and the development of mental disorder; but, obviously, this correlation is by far not high enough to account for the occurrence

of psychoses without any other contributing factor. The large majority of patients in our series, as well as in other series, did not receive an overdose of quinacrine. As to duration, we may refer to the patient in case 10, who received no less than 5.7 Gm. of quinacrine hydrochloride and yet recovered from his psychosis after two and a half days.

Another factor particularly stressed by Allen and co-workers [11] is the rate of elimination. It is well known that quinacrine is eliminated (through urine and feces) very slowly. According to Thonnard-Neumann and Ledoux,[34] quinacrine is eliminated within thirty-six days of the ingestion of the last dose. Field and Niven [26] found quinacrine in the urine longer than four weeks "only in a few instances." On the other hand, Kehar [35] detected traces of quinacrine as late as sixty-five days after the final dose. Allen and co-workers [11] called attention to the possibility that the normal accumulation of the drug may be increased, in certain cases, by deficient elimination and that this may account for the occurrence of toxic psychosis. However, no clinical observations are available to substantiate this theory. Damage to the kidneys or the liver (where quinacrine probably is accumulated) would have to be demonstrated as a complication in cases of quinacrine-treated malaria followed by psychosis. We did not find any indications to this effect either in our own series or in the literature. In the only case in which autopsy was performed (our case 4), nothing but congestion of the liver and kidneys was noted. With experimental quinacrine poisoning, pronounced hyperemia and toxic central injection of the liver and fatty degeneration of the renal tubules were found, obviously a side effect of fatal poisoning in the animal experiment (Molitor [24]).

In view of these observations, predispositional factors have to be considered. That one of them may be the preexisting malaria seems to be supported (1) by the fact that the incidence of quinacrine psychosis in our series is significantly higher with estivoautumnal malaria than with tertian malaria, a difference which may be considered as due to the higher toxicity of Plasmodium falciparum and (2) by the fact that quinacrine psychoses or psychoses due to other acridine dyes have not been observed in other than malarial patients, though these drugs have been used in treatment of other diseases, such as quinacrine for giardiasis or acriflavine for gonorrhea. However, it must be admitted that the total number of patients with conditions other than malaria treated

34. Thonnard-Neumann, E., and Ledoux, H. A.: The Treatment of Malaria with Erion (Atebrin): Report of Seventy-One Cases, in Twentieth Annual Report of the Medical Department of the United Fruit Company, Boston, 1931, p. 67.

35. Kehar, N. D.: The Influence of Food in the Stomach on the Absorption and Excretion of Atebrin, Rec. Malaria Survey, India **5**:405, 1935; Observations on the Absorption and Excretion of Atebrin, ibid. **5**:393, 1935.

with quinacrine has been exceedingly small as compared with the number of malarial patients. In addition, in 2 of our 19 patients no malaria parasites had been found in the blood; hence, the possibility exists that they did not have malaria at all.

Racial predisposition has been claimed by some observers, inasmuch as natives in East Asia seemed to have psychoses after treatment with quinacrine far more frequently than Europeans (Stitt [25]). However, no racial prevalence could be demonstrated in our series (see also Beckman [30]). Kingsbury [2] stated the belief that mental predisposition is an important factor, and Govindaswami [17] found that certain types of mentally deranged persons, as well as alcoholic (see also Whittingham [36]) and arteriosclerotic patients, do not tolerate the drug well. While our material does not actually confirm this assumption, it is quite probable that in psychopathic persons quinacrine psychosis is more prone to develop, just as are other forms of exogenic psychoses. We may refer to a recent observation of ours not included in this series, that of an alcoholic patient who had his first attack of delirium tremens immediately after the intake of 0.6 Gm. of quinacrine hydrochloride in two days, in treatment of mild estivoautumnal malaria. The possibility that quinacrine medication may have touched off the alcoholic delirium in this case cannot be denied. However, the clinical picture was that of delirium tremens, not of quinacrine psychosis.

With all this the idea, vague as it may be, that there may exist an individual idiosyncrasy to quinacrine, as pointed out by Turner,[37] cannot be disregarded.

There are two theories of the pathogenesis of the quinacrine psychosis, as pointed out by Kingsbury,[2] Molitor [24] and Banerjee.[8b] 1. Quinacrine destroys trophozoites faster than quinine and therefore may liberate malaria toxins in large amounts. Thus, this psychosis would actually be a malarial psychosis. 2. The toxic effect on the brain may be due to the toxicity of quinacrine itself, similar to that of the scopolamine group of drugs or of the encephalitis virus.

As to the first theory, Banerjee [8b] himself pointed out that all his cases were those of chronic malaria, in which cerebral stimulation is not known to occur. In cases of malarial infection of low intensity or in cases in which the onset of the psychosis is delayed, this theory becomes hardly tenable. It is possible, however, in view of the higher incidence of quinacrine psychosis in association with estivoautumnal malaria than with tertian malaria, that the infectious disease renders the brain susceptible to the toxic effect of quinacrine.

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36. Whittingham, H. E., and Discussion on Experience with Synthetic Drugs in the Treatment of Malaria, Proc. Roy. Soc. Med. **32**:1085 (July) 1939.

37. Turner, C. C.: The Neurologic and Psychiatric Manifestations of Malaria, South. M. J. **29**:578 (June) 1936.

The second theory appears to be better supported. In animal experiments Hecht [38] noted evidence of cerebral stimulation following lethal doses. According to Molitor,[24] quinacrine is only occasionally found in the cerebrospinal fluid, but it appears in the brain after injection of lethal doses. In the animal experiment toxic doses cause clonic convulsions. As previously mentioned, epileptiform seizures have also been observed clinically after injections of quinacrine. Of particular interest from the therapeutic point of view, to be discussed later, are experimental observations by Manifold,[39] who studied various acridine dyes for their relative toxicity to carbohydrate and pyruvate oxidation systems of brain tissue in the test tube. Among them, acriflavine was found to be highly toxic, even at very low concentrations, and other acridine dyes still toxic, though to a lesser extent. Apparently, quinacrine has not been tested with this method; however, being closely related to the other members of the acridine dye group, it might very well have the same form of toxicity, which consists in an inhibition of oxidative processes in the brain. This mechanism is essentially the same as that found to be active in cases of vitamin B deficiency, a fact which would account for the similarity of psychiatric pictures of quinacrine and deficiency psychoses.

As to treatment, we found valuable high doses of concentrated vitamin B complex, particularly thiamine hydrochloride and nicotinic acid, not only because there is a sound theoretic basis for it (Manifold [39]) but because we observed dramatic results at least in 2 of our cases (15 and 16), in which the psychosis had been going on for five and six days, respectively, and cleared up one to two days after the administration of vitamin B preparations. While it is true that most patients recover spontaneously from the psychosis, treatment does not appear unnecessary in view of the fact that occasionally quinacrine psychosis may last several weeks.

Our use of vitamins followed the routine for treatment of alcoholic psychosis:

Thiamine hydrochloride, 50 mg. intravenously, four times a day
Thiamine hydrochloride tablets, 10 mg., three times a day
Nicotinic acid, 50 mg., three times a day
Vitamin B complex capsules,[39a] 2, three times a day

In addition, fluids should be forced, in order to speed up elimination of the drug. For the same reason, the bowels should be kept open, both during and after the treatment.

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38. Hecht, G.: Pharmakologisches über Atebrin, Arch. f. exper. Path. u. Pharmakol. **170**:328, 1933.

39. Manifold, M. C.: The Effect of Certain Antiseptics on the Respiration of Brain Tissues in Vitro, Brit. J. Exper. Path. **22**:111 (June) 1941.

39a. Each capsule contained 5 mg. of thiamine hydrochloride, 25 mg. of riboflavin and 25 mg. of nicotinamide.

SUMMARY

A series of 19 cases of toxic psychosis following quinacrine treatment of malaria, as observed in Gorgas Hospital from 1935 to 1943, is reported.

The incidence of quinacrine psychosis in Gorgas Hospital was 0.39 per cent of all quinacrine-treated patients, or about 1 out of 250 so treated. It appeared to be moderately higher with estivoautumnal than with tertian malaria.

The clinical characteristics of our observations are described and compared with those in 43 cases previously published by other observers. Case histories and postmortem observations are given in 1 fatal case of quinacrine psychosis and in 1 case of quinacrine psychosis superimposed on early dementia paralytica.

The etiologic factor responsible for quinacrine psychosis is probably to be found either in an individual hypersensitivity to the drug or, in some cases, in constitutional psychopathy. Toxic damage to the central nervous system caused by malaria seems to be a contributing factor. The effect of overdosage of the drug remains doubtful. The pathogenesis of quinacrine psychosis is probably determined by hypersensitivity to the drug and its specific toxic effect on brain tissue previously sensitized by malarial infection.

Prevention of quinacrine psychosis consists in recognizing that a certain few persons are probably hypersensitive to the drug. The dosage should rarely exceed 2.8 Gm. in one course of treatment, especially when the therapeutic effect can be attained with a lower dose. Parenteral, in particular intravenous, administration should be limited to cases in which therapeutic results cannot be obtained otherwise. For treatment, high doses of vitamin B preparations and forced intake of fluids are recommended. The prognosis is favorable, with few exceptions. No chronic mental ailment has been observed to develop from this condition.

PREVENTION AND TREATMENT

Quinacrine has proved, for the last ten years, to be such a valuable addition to medical resources in combating malaria that possible complications arising during treatment, even if they were somewhat more frequent than they actually are, would not justify its abandonment. An incidence of 1 in 250 treated patients, such as that of quinacrine psychosis, is certainly not serious, the more so as the mental disorder is usually of short duration, ending in recovery. Still, it deserves attention, and whatever may be possible to reduce it should be done. In the first place, the dosage and timing of quinacrine treatment must be considered. We have hardly any positive evidence to prove that overdosage per se is an essential factor responsible for the development

of quinacrine psychoses, considering the fact that in the large majority of cases in the literature, as well as in our series, the amounts of quinacrine given were very moderate. However, taking it for granted that a small number of persons appear to be hypersensitive to this drug, and that these hypersensitive patients are more likely to respond with psychotic symptoms to higher than to lower doses, we suggest moderate conservatism with respect to dosage and timing of quinacrine treatment. The amount of 2.8 Gm. given in one week, as recommended by the War Department, Circular Letter no. 153,[40] ought to be considered as the upper limit. Experience shows that a dose of 2 Gm., or even less, is usually sufficient for successful treatment of the clinical attack. As it seems that parenteral methods of treatment are more likely to bring on psychoses than oral ones, they ought to be used only when the seriousness of the case requires it. These precautions as to dosage, form of medication and timing ought to be considered carefully, particularly in cases in which the history gives evidence of psychopathy or chronic alcoholism.

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40. The Drug Treatment of Malaria, Suppressive and Clinical, United States War Department, Circular Letter no. 15, Washington, D. C., Government Printing Office, August 1943.

NYSTAGMOID MOVEMENTS AND VISUAL PERCEPTION

Their Interrelation in Monocular Diplopia

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IN A previous communication one of us (M. B. B.) reported 4 cases of monocular diplopia and polyopia in patients with disease of the brain.[1] Although each case presented a different clinical and pathologic problem, there were certain features which all had in common: The double or multiple vision was most pronounced on prolonged or close fixation. Two of the patients, who were studied in detail during the period when the illusions were manifest, complained of multiple image formation only after prolonged fixation on an object. Furthermore, the diplopia and polyopia seemed to be confined to the macular field of vision. Since the act of close fixation is usually associated with an increase in ocular movements, it was felt that the latter might in some way be related to the phenomenon of monocular diplopia and polyopia. Kubie and Beckmann [2] found that increased ocular movements resulted in diplopia (presumably binocular and without palsies of extraocular muscles) in patients with lesions of the optic chiasm. In other words, an alteration in the oculomotor status (increased ocular movements) is associated with a change in visual perception (multiple images). Theoretically, a decrease in movements of the eyes should also be associated with a change in visual perception.

In order to test these hypotheses, 2 cases were studied. In the first case, that of a patient with encephalitis, various methods were employed to assess the degree of increase in ocular movements which occurred during fixation and during the appearance of monocular diplopia. In the second case special tests of visual perception were carried out after the ocular movements (congenital nystagmus) had been temporarily

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1. Bender, M. B.: Monocular Diplopia and Polyopia of Cerebral Origin, Arch. Neurol. & Psychiat. **54**:323-338 (Nov.-Dec.) 1945.

2. Kubie, L. S., and Beckmann, J. W.: Diplopia Without Extra-Ocular Palsies, Caused by Heteronymous Defects in Visual Fields Associated with Defective Macular Vision, Brain **52**:317-333, 1929.

abolished by the injection of sodium amytal.[3] The relationship between ocular unrest and formation of multiple images could thus be investigated in two ways: (1) by direct observation of the movements of the eyes which occur during an existing diplopia, and (2) through induction of monocular diplopia (by altering the subject's ocular movements with a drug).

METHOD

It has long been known that ocular movements are present during fixation in normal subjects. These movements can easily be demonstrated with the help of the standard laboratory methods (Dodge[4]; Judd and associates[5]). According to the measurements of Adler and Fliegelman,[6] the movements represent a fine tremor rather than excursions of a nystagmoid character. Their extent is well below 1 degree. In cases of monocular diplopia it is assumed that instability of ocular movements during periods of fixation leads to somewhat wider excursions.

These relatively extensive movements should then become manifest even without the use of complicated apparatus. Many of the early investigations on movements of the eyes were carried out in a simple clinical setting. Such observations, even if not exact, may be sufficiently suggestive to make a preliminary test of certain hypotheses possible. Among these older methods there are at least three which are promising in a clinical situation: (1) the so-called peephole method, (2) the mirror method and (3) the after-image method. The first two procedures enable the experimenter to observe directly any gross ocular movements in a subject. The third method is unique in that the subject himself observes and describes the movements of his eyes during the act of viewing an object. It requires of the subject a particular degree of cooperativeness and intelligence. But given these conditions, it is definitely superior to the first two approaches. It was used extensively by von Helmholtz.[7]

1. The peephole method (Miles[8]) consists in observing the subject's eye through a small hole in a paper he is reading or a picture he is

3. Bender, M. B.: Effects of Barbiturates on Ocular Movements (Nystagmus), to be published.

4. Dodge, R.: An Experimental Study of Visual Fixation, Psychol. Monogr. **35**:1-95, 1907.

5. Judd, C. H.; McAllister, C. N., and Steele, W. M.: Introduction to a Series of Studies of Eye Movements by Means of Kinetoscopic Photographs, Psychol. Monogr. **29**:1-16, 1905.

6. Adler, F. H., and Fliegelman, M.: Influence of Fixation on the Visual Acuity, Arch. Ophth. **12**:475-483 (Oct.) 1934.

7. von Helmholtz, H.: Handbuch der physiologischen Optik, Leipzig, L. Voss, 1866.

8. Miles, W. R.: The Peep-Hole Method for Observing Eye Movements in Reading, J. Gen. Psychol. **1**:373-374, 1928.

scanning. The experimenter is seated behind the paper, and partly concealed by it, with his face turned toward the subject.

2. The mirror method is more frequently used in ophthalmologic and neurologic examinations. A plane mirror is placed beside the object which is being inspected, and the experimenter watches the subject's ocular movements in the mirror.

3. The after-image method consists in giving the subject a small, distinct after-image for the eye which is to be observed. The subject then views the test object; as long as the after-image persists, its excursions over and around the test object define the subject's ocular movements to the subject himself provided these movements are not too rapid.

OBSERVATIONS

All three methods for direct observation of ocular movements were used in our first case. The patient, a seaman first class, aged 21, had been studied over a period of four months after his attack of acute encephalitis following measles, which had led initially to a parkinsonian state. As the paralysis agitans subsided, only a few disturbances remained, primarily centered around the patient's vision.

Prior to his induction into the United States Navy the patient had studied chemistry and had won high academic honors. He always had a vivid after-imagery and had made spontaneous observations on these phenomena. To the patient's distress, this after-imagery was completely lost after the acute stage of his disease, and only two months later did it gradually return.

During his period of recovery the after-images deviated from the normal in the same measure as did the patient's visual functions in general. After an initial phase bordering on visual agnosia had been overcome, the patient's visual organization was characterized by an extreme amount of fluctuation and obscuration. The specific perceptual disturbances can perhaps be subsumed most adequately under the concept of a loss in perceptual constancies, particularly constancy of size. When objects were exhibited to the patient and then gradually moved away from him, their apparent size decreased much more rapidly than the usual constancy effect would allow. At the same time, the patient's after-imagery (when he regained it) did not follow Emmert's law; that is, the images did not change in apparent size when projected against backgrounds of varying distance.[9]

However, the most outstanding abnormality was the patient's monocular diplopia, already described.[1] The patient had a congenital convergent strabismus of the left eye, and vision in this eye had always been poor (amblyopia ex anopsia). He had never experienced any diplopia. His visual fields were intact. Yet, two and a half months after his acute illness, monocular diplopia developed in the patient's better, or apparently normal, eye (right eye), although it was also found, but less constantly, in the left eye. The double image was always incomplete, displaced to the left and slightly below the original. When the test object was moved away from the patient, the distance between the double image

9. The connection between the phenomena summarized by Emmert's law and the effects of size constancy has been formulated by Boring (Am. J. Psychol. **53**:293-295, 1940).

and the original image showed a slight increase, and the double image became less complete. Even at that time the patient stated occasionally that he could see a faint after-image and the double image of an object simultaneously.

Throughout his period of recovery our patient observed the gradual change in his condition and gave detailed oral and written reports. There were no indications of a magnification or a minimization of symptoms. When he submitted to the experiments which are described in the next paragraph, his after-imagery had almost completely returned, while his monocular diplopia still persisted. For this reason, although all three methods of observation of ocular movements were employed, special emphasis was placed on the third, the after-image, method. (The patient's left eye was covered throughout the experimental sessions.)

Peephole Method.—During maintained fixation this method was not sufficiently adequate to permit conclusive observations, regardless of whether the patient reported single or double vision.

When he read a newspaper article (held at 12 inches [30 cm.] from the eyes, the lines being 2 inches long [5 cm.] and ⅛ inch [.32 cm.] apart, the patient's eye gave the impression of sluggish and somewhat excessive saccadic movements, superimposed on continual horizontal nystagmoid movements. This nystagmus was so fine that it was impossible for the observer to decide whether the nystagmus was of equal extent to the right and to the left.

Mirror Method.—1. Fixation: As long as the patient reported single vision, his eye appeared fairly steady. After from two to five seconds there was a slight, but brisk, shift of the right eye to the patient's right. Then the fine lateral nystagmus was noted. At the same time the patient announced the appearance of a double image.

2. Reading: Observations through mirrors revealed the rather sluggish saccadic movements of the eye from left to right. The fine lateral nystagmus was only occasionally noticeable. If the left eye was temporarily uncovered, it could be seen that it frequently "lagged" behind the right.

After-Image Method.—The patient's ocular movements during fixation were observed by the patient himself by means of the after-image of a small, luminous disk supplied by the ophthalmoscope. Preceding each trial, the patient's eye was stimulated by shining the beam of the lit ophthalmoscope into the right eye. After the initial trials, the patient held the ophthalmoscope himself, since ocular movements during stimulation were minimized in this way. However, regardless of any movements of the eyes which might have occurred during stimulation, a distinct disk-shaped after-image was obtained with periods of exposure as long as forty-five seconds. Immediately after stimulation, the patient was asked to fix the center of a red cross on white paper, 12 inches from his right eye. The arms of the cross measured 1 inch (2.54 cm.) each. The patient was urged to fixate as steadily as possible (with his chin locked in his hands to minimize head movements). He was told to report the relative position of the after-image to the center of the cross, as well as any shifts in the position of the after-image. For obvious reasons, he was kept unaware of the fact that these excursions of the after-image were indications of his ocular movements. The patient was further instructed to report immediately the appearance of the double image of the cross—whether it appeared instantly or after a lag—and to observe the shifts, if any, in the position of the double image relative to the center of the cross. (These detailed instructions were given the patient gradually during the first three trials. At first he was asked only to fix the center of the cross

and to report all movements of the after-image.) After a short period of practice, the patient seemed to have little difficulty in reporting on both after-image and double image in relation to his point of fixation. This may be due to the fact that both remained within or close to foveal vision—indeed, everything took place within a range corresponding to an angular distance of slightly less than 8 degrees.

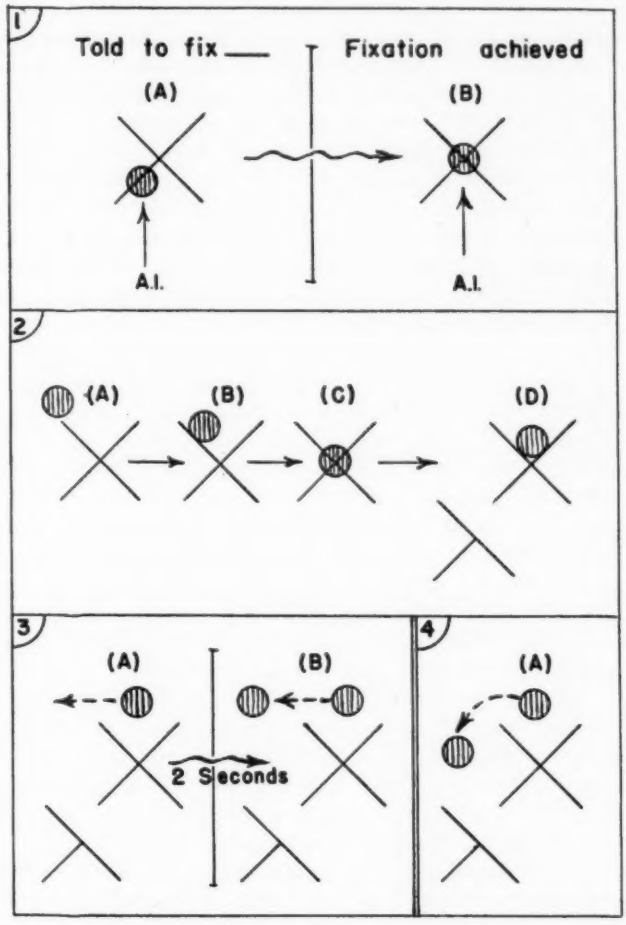

Fig. 1.—*1 to 4:* patient's after-images (represented by disks) in relation to the cross. (*1, A*) The patient is instructed to fix the center of the cross; (*B*) fixation is achieved; the after-image has moved into the center of the cross. (*2 A*) The patient is again attempting to fix; the after-image moves through *B* and *C* into the center. As soon as the center has been reached, the double image appears (*D*). (*3* and *4*) Periodic excursions of the after-image occur to the left; the after-image traverses a distance equal to that between the original and the double image; then it is seen "suddenly" back in the center, or slightly above the cross.

First Trial: The patient observed how his after-image moved into the center of the cross, i. e., the intial adjustment of fixation. At the same time, the early phases of flight of colors in the after-image were reported (fig. 1*1*).

Second Trial (fig. 1 *2*): Although the patient was instructed to attend only to the after-image, its movements and changes in color, he spontaneously announced the appearance of a double image. It was incomplete, as usual for this patient, and appeared to the lower left of the original cross, ¾ inch (1.9 cm.) away from it in the patient's estimation. (This corresponds to an angle of about 4 degrees.) From the illustration it will appear that the double image was reported only after fixation had been achieved, that is, as soon as the after-image had come to a first (temporary) rest in the center of the cross.

When asked specifically whether he thought this double image had been there "right away" or whether it appeared only at the time he announced it, our patient could not reply with certainty. He thought that the double image was instantly there, as soon as he looked at the cross. However, he was not sure whether this was true in all trials. On the other hand, he was definite in his statement that the double image did not move at all, whereas the after-image moved "almost constantly." The after-image came in "from above and from the left," down toward the center of the cross. Then, the patient said, the after-image was "suddenly" off center again (usually above) and moved back on or near the center. Then this cycle recurred, repeating itself about half a dozen times, until the after-image faded out.

Third Trial: The same results were obtained as on the previous trial. Again, the patient reported a double image after he had stated that the after-image had "reached" the center of the cross, but he was not certain about time relationships. Since the patient had to report verbally on all these movements while the movements were still going on, nothing but a rough estimate of the time element could be obtained (fig. 1 *2*).

Fourth Trial: The patient saw his after-image immediately, above the center of the cross and to the left. By the time it moved into the center of the cross, and not before, the double image became visible to the lower left.

Fifth Trial: The after-image was immediately in the center of the cross; the double image was announced as appearing instantly, and it did not move. (The patient had been asked to pay special attention to whether the double image moved with the after-image, in a different way or not at all.) Within "less than a second" the after-image was seen on top of the cross (fig. 1 *3*), and then it moved to the left. A second later the after-image was reported at the same height as the double image, that is, above the double image but at the same distance from the vertical line drawn through the center of the cross, whereas the double image remained stationary (fig. 1 *3*).

Sixth Trial: The after-image appeared to move first to the left in a slight downward curve, but, again, it came to a stop at the same height as did the double image (fig. 1 *4*). After the first reported excursion of the after-image in this trial, the patient specified six more excursions (in retrospect) for the next two and a half seconds. The after-image now moved steadily, but swiftly, along a horizontal (linear) path to the left, "always stopping when it got into the same vertical line with the double image" (same as fig. 1 *3*). The double image remained stationary throughout. As one would expect, the patient did not know when and how his after-image got back in or near the center of the cross after each horizontal excursion.

Throughout these experiments, the widest excursions of the after-image corresponded to an angular distance of 8 degrees. Assuming 2 degrees as the maximum diameter of the fovea centralis, it is to be noted that the nystagmoid movements during fixation carried the image periodically into the pericentral area. Varying values have been given for the "fixation tremor" in normal

subjects, but Adler and Fliegelman's measurements [6] showed them to be about 25 minutes, and Duke-Elder's [11] review of the experimental literature on the subject gives 4 minutes as the average. Our patient's change in ocular position thus must have been much greater than that observed in normal subjects.

In spite of this, the patient was neither directly nor indirectly aware of these movements. The weak after-image moved with his eye, describing, as in normal subjects, the full amount of ocular movement. Conversely, the continual retinal displacements of the stimulus object (due to the unrest during fixation) were perceived by the patient not as oscillation of one object, but as a stationary double configuration. The only motion perceived was that of the after-image, and therefore the latter actually defined the full amount of ocular movements as projected into space. These relationships could easily be demonstrated: As soon as the situation was changed by making the patient conscious of his ocular movements, the double image disappeared. The patient was instructed to shift his eye and try to make the double image move on its background in the same manner as the after-image had been reported to move. The result was an immediate disappearance of the double image, while the after-image remained visible, although moving in erratic fashion, since the patient had become aware of gross movement of his eyes and the "unconscious" nystagmoid movements had been stopped, or at least modified.

Comment.—The observations on this patient demonstrated (*a*) an increased fixation tremor and (*b*) a concomitant appearance of monocular diplopia. The diplopia set in as soon as the nystagmoid movements began. The slow phase was always in the direction of the double image, and the distance between the two images was equal to the angular distance described by the excursions. Finally, in comparison with the ocular unrest during fixation in normal subjects, the patient's fixation tremor was definitely increased, although it did not reach the extent of a regular nystagmus.[12]

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10. Footnote deleted by author.

11. Duke-Elder, W. S.: Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1938, vol. 1, pp. xxxi and 1137.

12. This fixation tremor might help to explain the incompleteness of the double image. One could argue that a greater extent of excursions would have led to the formation of two complete double images, and an even greater extent to the appearance of polyopic phenomena. However, one does not know enough about the corresponding cortical processes. Closely adjacent retinal images are probably represented on the striate cortex by closely adjacent excitation processes, even though this representation exists only in a dynamic sense. The occurrence of mutual attraction and interference (on the cortical level) between such closely adjacent percepts has been shown by Werner (Am. J. Psychol. **53**:418-423, 1940), who demonstrated these effects by means of a rapidly alternating separate presentation to each eye. Under pathologic conditions, rivalry can be demonstrated even for a single eye (as a rivalry between the two half-fields). The incompleteness of the double image would thus appear as an incomplete fusion, which might well be what Goldstein [14] meant by assuming abnormal "diffusion" on the visual cortex. In this connection, it should be noted that the threshold for flicker and fusion were notably reduced for this patient, while he showed an augmentation in his contrast phenomena, particularly internal contrast.

It will be recalled that the patient had a congenital convergent squint. Although this condition did not lead to binocular diplopia until after his encephalitis, it is conceivable that it supplied a latent disposition for a specific form of diplopia and concomitant ocular unrest.[13] The excursions of his right eye during fixation were primarily to the left, and the double image was consistently referred to the left, or, in other words, to the patient's weak side.

The nystagmoid movements to the left were increased whenever objects under fixation were moved farther away from the patient, and thereby decreased in size on the retina. Strong contrast—internal and external contrast—likewise made steady fixation more difficult for the patient. Fixation is primarily a function of the occipital lobe, and it is not unlikely that both the diplopia and the unsteadiness of the eyes during fixation were results of one and the same disturbance in function of the occipital lobe. A generalized disturbance in visual functioning on this highest level had been found for this patient in other respects, as, for instance, in the impairment of size constancy.

Generalized disturbances in perception were postulated by Goldstein[14] in his own cases of monocular diplopia. In keeping with his "field theory" of cortical function, he assumed that injured or diseased cortex is characterized by an abnormal "diffusion" of figural processes. If this spread of the configuration over its background becomes extensive enough to involve areas with different space values, the formation of double or multiple images, will result. Our own direct observations on the role of ocular movements in the appearance of monocular diplopia do not detract from such a diffusion theory, nor do they contribute to its confirmation.

In point of fact, our observations show only a concomitance of irregular movements of the eyes with the occurrence of monocular

13. Bielschowsky's *locus classicus* (Arch. f. Ophth. **44**:143, 1898) on monocular diplopia associated with strabismus does not consider the role played by ocular movements. Cass (Brit. J. Ophth. **25**:565, 1941) found that he was able to induce monocular diplopia in cases of congenital squint by a method of flicker. This procedure, he asserted, stimulated the true and the false macula in rapid succession and thus produced diplopia in the squinted eye. Similar to this artificial situation is the spontaneous monocular diplopia, which has been observed at times in hemianoptic persons during the emergence of a pseudofovea, when retinal correspondence was in the process of restructuring itself. In our own cases of monocular diplopia, the emergence or existence of a permanent pseudofovea did not seem to be a necessary condition. However, the increased ocular movements during fixation in our patients carried the image periodically over regions of different excitability.

14. Goldstein, K.: Ueber monokuläre Doppelbilder: Ihre Entstehung und Bedeutung für die Theorie von der Funktion des Nervensystems, Jahrb. f. Psychiat. **51**:16-38, 1934.

diplopia. One is tempted to say that the ocular movements are the "cause" of the diplopia, but it could just as well be argued that the diplopia occurs and that the patient therefore begins instantly to shift his eyes involuntarily back and forth between the true and the "false" image. In the light of our observations in this, and in the following, case, we think, rather, of the two phenomena as simultaneous: The disturbances in movement and in perception are only two aspects of the same disruption in function, just as normal perception depends on normal motion and vice versa.

Case 2.—While in case 1 monocular diplopia developed after an acute infectious process, in our second case, that of a patient with congenital nystagmus, monocular diplopia developed under artificial conditions.

The patient, a 23 year old Marine, was admitted to the hospital because of dizziness and a sense of weakness. The general physical and neurologic examinations revealed nothing of significance except for nystagmus. The nystagmus was pronounced enough to arouse the attention even of the casual onlooker. On examination it was found to be spontaneous, continual, irregular and almost exclusively in the horizontal plane. Occasionally, a slight rotatory component (clockwise) could be noted. The horizontal excursions of the eyes were more pronounced to the right than to the left. However, the difference was too small to be noted on direct observation; it was found by use of the slit lamp. It was further noted that the nystagmoid movements of the right eye were less pronounced than those of the left; that is, they covered less distance and were correspondingly slower than those of the left eye. But since the excursions were strictly synchronous, the difference between the two eyes became noticeable only on observation through the telescope.

In both extreme lateral positions the nystagmus was definitely less pronounced than on forward gaze. This was more noticeable when the patient looked to the right. For this reason, the patient had acquired a habit of inspecting objects "out of the corner of his eyes." Whenever he wanted to see finer details of objects, he brought his eyes into the right extreme lateral position. He complained about this "bad habit" and said that when he was following movies on the screen his head was "pulled" to the left and his eyes were shifted to the right, where he could see better.[15]

Actually, it could be shown that his acuity in binocular vision and straight forward gaze on the Snellen chart was inferior (6/20 in each eye) to the acuity in the extreme lateral position (10/20 in each eye), in which the nystagmoid movements were minimized. The lens system itself appeared intact, as were the external ocular muscles. There were no defects in the visual fields.

However, the patient followed this "pull" only under special circumstances, e. g., during prolonged fixation or while attempting to recognize persons at a distance. It was definitely not an abnormal tonic pull to either side. There were no symptoms of cerebellar or labyrinthine involvement. Efficiency in the left extreme lateral position was equal to the one in the right. After repeated Bárány turning tests, the patient experienced vertigo but showed only his usual nystagmus on

15. In another case of (presumably) congenital nystagmus analogous behavior was found. In that instance the nystagmus was primarily upward and downward, and the patient had "learned" to minimize this nystagmus, and hence to improve his vision, by rolling both eyes slightly upward during prolonged fixation.

forward gaze, without increase in excursions or change in pattern. Nystagmus in the extreme lateral position was increased. However, there was little, if any, past pointing.

Induced Opticomotor Nystagmus.—On stimulation with a rotating striped drum the patient did not show any opticokinetic nystagmus, regardless of the direction in which the stripes were moving. However, thresholds for flicker and fusion were greatly reduced when the stripes moved at right angles to the patient's horizontal nystagmus.

Status of Patient's Visual Perceptions Before Experiment.—In spite of the extreme irregular spontaneous movements of his eyes, this patient had achieved a surprisingly adequate visual performance.[16] He had never had any diplopia. "Blurring" occurred occasionally while reading, and he stated that "the lines became all one black bar." A single light in the dark would appear as a "neon sign" (oriented horizontally, like his nystagmus), especially if the patient himself were moving.

After-images were difficult to obtain. A drawing of the American flag in complementary colors was seen as a light, colorless field, without detail, shrinking and expanding at a rapidly fluctuating rate. Stimulation with a strong disk of light (100 watt bulb held at 1 inch from the eyeball for five seconds) resulted in the perception of a horizontal luminous bar (also described as a "neon sign" by the patient), again growing longer and shorter. There was also a rapid alternation in colors (blue, green, blue, green, etc.) which was synchronous with the changes in the length of the after-image.

Except for horizontal elongation of the after-image and of single points of light in a dark field, the patient did not show any distortion effects in his visual perceptions. A heavy black *L* on a white card remained equilateral and unchanged on prolonged fixation, in spite of changes in position. A fine dark line on a white ground never appeared double, although when it was held in the vertical position the patient complained that he saw dark streaks, "shadowy," parallel to each other and shooting horizontally across the vertical line.

Reversible figures, such as the Schröder staircase and the double face, were seen at normal rates of alternation.

However, in judging lengths of lines at varying distances, the patient showed an increasing tendency to underestimate length with increase in distance. The difficulty was more noticeable with horizontal than with vertical lines. His performance was suggestive of an abnormally low degree of size constancy, particularly in the horizontal meridian.

After this cursory inventory of the patient's visual functioning, the impression was gained that for all practical purposes his nystagmus had to be considered as congenital.[17] This explains the amount of adaptation achieved. On superficial examination at least, the continuous horizontal deviations of the patient's eyes seemed barely to affect the appearance which his world had for him. Under these conditions, the question presented itself: What would happen to his visual organization if this nystagmus could be arrested at least temporarily, as with the use of barbiturates? Barbiturates have been found to abolish various forms of nystagmus,

16. By contrast, in patients whose nystagmus appears when one eye is closed or binocular vision is interrupted (latent nystagmus), vision becomes much impaired and objects appear to jump.

17. The clinical history showed that during the first years in school the patient was repeatedly sent to the family doctor and ophthalmologist because of this nystagmus.

especially the congenital form.[4] This abolition is temporary, lasting from two to three hours.

Experimental Arrest of Patient's Nystagmus.—The patient was given an injection of 0.3 Gm. of sodium amytal by vein, and the following observations were made:

Three Minutes: Most of the spontaneous horizontal nystagmus evident on direct gaze disappeared, and there were coarse, slow nystagmoid movements only when the eyes were turned in extreme lateral position.

Nine Minutes: There was no nystagmus on convergence, fixation, upward gaze or downward gaze, but there was pronounced nystagmus in the extreme lateral position. The status preceding the injection was thus completely reversed. The generalized effects of the barbiturate were noticeable but not pronounced. The patient felt "high," or "punch drunk," and asked whether he would have a hangover.

Fourteen Minutes: He stated, "I hardly feel my eyes from all that shot."

Seventeen Minutes: The nystagmus in the extreme lateral position became less pronounced.

Twenty-One Minutes: A slight, oscillatory tremor of both eyes reappeared on forward gaze. From then on, for eighty minutes, this nystagmus continued to fluctuate in extent, increasing and decreasing at five to ten minute intervals but becoming more pronounced each time. The nystagmus in the extreme lateral position showed a concomitant decrease.

Twenty-Nine Minutes: The patient said, "My eyes feel better than before the shot. Are the movements coming back?" (He showed some nystagmus on forward gaze at this point.)

Thirty-Eight Minutes: The patient rubbed his eyes vigorously, frequently blinking, and complained that his eyes hurt badly. "It's getting foggy again—things look like before the shot" (conspicuous nystagmus).

Forty-One Minutes: He said: "I could see better after that shot—now it comes back."

Forty-Three Minutes: Full nystagmus was present on forward gaze, for the first time since the injection.

Disturbances in Visual Perceptions During Period of Reappearance of the Nystagmus.—Forty-three minutes after the initial injection, when the full nystagmus had returned for the first time, the patient looked at a pencil held at arm's length before him. He said it was getting "wider." He also stated that the doctor's face was "broad—like a fat man's."

Special examinations revealed the following disturbances:

1. *Perception of Single Vertical Lines*: A straight vertical line drawn with a pen on white paper at 2 feet (60 cm.) from the patient elicited this comment, "It's thick and stays thick—a half-inch at least." A heavy black line (about ⅜ inch [.96 cm.] thick), printed on white cardboard, was exhibited in vertical orientation, 2 feet from the patient. The patient insisted that this line, too, was ½ inch (12.7 mm.) thick. A minute later he exclaimed, "Now the line is getting thinner all the time."

2. *Single Lines, Rotated into Horizontal Positions:* The printed line was again shown to the patient, in the same vertical position, a minute and forty seconds after it seemed to the patient to get thinner and thinner. The patient said again that it appeared to be ½ inch thick. At this point the card was rotated through 90 degrees, until the heavy black line came into horizontal position. The patient reported that the line had become thin, but "it's about a yard long." With the same card in a slanted position (45 degrees above the horizontal), the patient drew a trapezoid

thickest on its upper end (fig. 2 *A*). Instructed to shift his fixation to the lower end of the line, he reported that the trapezoid had become thickest at its lower end (fig. 2 *B*).

3. Two Lines: Two lines of equal length at right angles to each other, forming an L, were seen by the patient as distinctly unequal, the vertical line being short and thick, the horizontal line thin and long (patient's drawing, fig. 2 *C*).

4. Closed Figures: A heavy black circle printed on a white card (thickness of periphery, ⅛ inch) looked to the patient "like a football," that is, broadened in the horizontal dimension (patient's drawing, fig. 2 *D*). A triangle appeared distorted in a similar, though less symmetric, fashion, indicating a greater amount of distortion (elongation) to the right (patient's drawing, fig. 2 *E*).[18]

5. After-Images: Only an incomplete, light after-field, without detail and color, was obtained after repeated exposure of an American flag, drawn in the complementary colors. The patient complained that he could not maintain fixation

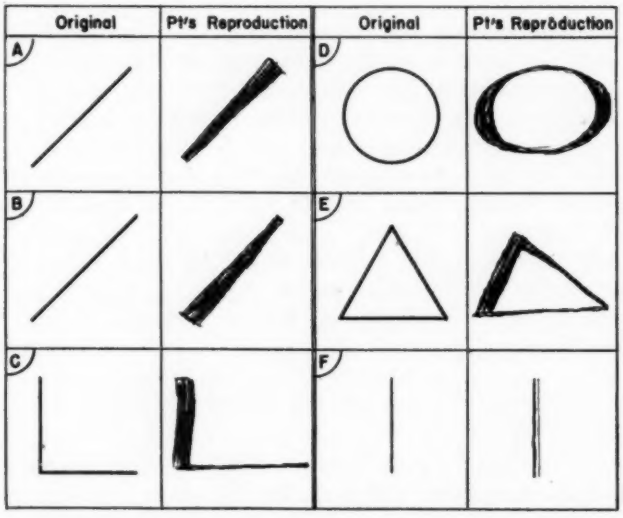

Fig. 2.—Distortions of perceptions during the period of recovery from sodium amytal (patient's own drawings). The patient was fully aware of these distortions. *A*, fixation on upper (right) end of line; *B*, fixation on lower (left) end of line.

during exposure. The lines of stars would "run together" and black out—"just like one of these reading blurs," of which he had complained before the experiment. After prolonged fixation the whole flag "blacked out" at five second intervals, and the patient felt compelled to look away.

6. Reversible Figures: While the after-imagery was not improved over the preexperimental status, the patient showed an increased flexibility in obtaining the Schröder staircase effect. The first reversal was reported almost immediately, with rapid shifts following in cycles of three to five seconds. With signs of excitement, which increased his usual difficulties in verbalizing what he saw, the patient

18. All these perceptual disturbances are clearly related to the patient's horizontal nystagmus. In 1 instance (the triangle fig. 2 *E*) we even found a greater distortion to the right, in keeping with the fact that the greater excursions of the patient's eyes were to the right during nystagmus.

attempted to describe a peculiar effect: The "bottom line" of the staircase appeared lengthened and shortened in comcomitance with the shifts in perspective. It appeared long when the figure was seen right side up and short when it appeared upside down.

7. Monocular Diplopia: Ninety minutes after the injection of the first cubic centimeter of sodium amytal, the patient was again confronted with a straight vertical line drawn with pen on white paper. No "broadening" of the line was reported. After ten seconds the line was slowly rotated about 45 degrees out of the verticle toward the patient's left. The patient reported that another line, fainter than the first one, "jumped out" to the left of the original. The two lines were described as close together and "quivering." They were seen binocularly and monocularly with each eye. Their appearance and relative distance remained unchanged in binocular and in monocular vision. It was also noted that changes in distance of the stimulus from the patient's eyes did not induce changes in relative distance of the original image and the double image. But the diplopia in itself was evanescent. Beyond the range of 2½ feet (76 cm.) it could not be obtained. When the original line was rotated out of the vertical, there were no changes. Both lines stayed parallel, "about 0.5 mm. apart," and remained in this orientation even after the horizontal had been reached. The line appeared still distinctly double, with the fainter, double, image below the original image (patient's drawing, fig. 2 *F*). However, after he had maintained fixation (at a distance of 16 inches [40 cm.]) for fifteen seconds with the original line in its horizontal position, the images grew "fuzzy" and became single.

The experiments were terminated one hundred minutes after the injection. At that time the patient was relaxed, and his nystagmus had again decreased considerably. Apparently, the fluctuations in oculomotor function, which had been in evidence throughout the period of recovery from the effects of the drug, were still persisting. Casual examination showed absence of diplopia and a recurrence in the "thickening" of vertical lines.

Comment.—These observations clearly indicate that the patient's changes in visual perception were more or less directly related to his ocular movements, i. e., horizontal nystagmus. The observations during the period of reappearance of the nystagmus could be brought under a few headings: (*a*) lengthening of horizontal lines; (*b*) broadening of vertical lines; (*c*) corresponding distortions, simultaneously in the horizontal and the vertical direction, for closed figures, and, finally, (*d*) monocular diplopia.[19]

19. The diplopia itself is just as clearly related to the patient's ocular movements as that in our first case, for the double image disappeared after a latency of fifteen seconds when the original line was rotated into the plane of the nystagmus, and it likewise disappeared when the nystagmus decreased.

But, even more than in the first case, the diplopia was only one symptom among a number of deviations from normal perception. For this reason, the rare instance of "nystagmus diplopia" cannot be understood without an attempt to define its place among these more general disturbances, for they not only preceded the monocular diplopia during our experiment but persisted, in the sense that they could be evoked again, later on, under special conditions. It therefore remains to be seen in which way these general disturbances of perception were related to the transient diplopia and why they appeared successively under the conditions of our experiment.

In contrast to the patient's performance before the experiment, these disturbances indicated a much closer correspondence between the shape of the patient's perceptions and the pattern of retinal stimulations. The latter, the "proximal" stimuli of Koffka,[20] were originally embedded in a relatively normal functional organization, which restructured the incoming stimulus patterns into single, and fairly undistorted, percepts. This was achieved at the price of acuity and with some fluctuation; but, in return, our patient did not see objects as he ought to have seen them. That is, he did not see them double or multiple or otherwise distorted according to the continual horizontal movements of his eyes. Neither did his visual objects appear to move, except under highly artificial conditions in which the usual points of reference were absent (e. g., a single point of light in the dark). An overestimation of the horizontal dimension in judging shapes, sizes and distances may have been present before the experiment. But our tests at that time failed to reveal its extent. That the patient's vision was always beset with difficulties became evident in his casual remarks during the period immediately following the abolition of his nystagmus. Then he complained that with the recurrence of the ocular movements his vision became foggy "again." But it is reasonable to assume that the patient himself became aware of such a generalized impairment of his vision only by means of the contrast with a temporarily improved performance after administration of sodium amytal.[21] On the whole, our patient had succeeded in building up a perceptual framework in which the ambiguous stimuli from his retina obtained definite meaning. On the other hand, he showed certain deficiencies in this framework which made it different from the one found in the visual organization of normal subjects. His ability to maintain constancies for size and form over normal ranges was impaired.

Under the effect of the barbiturate, the patient's nystagmus disappeared, and thus his vision became even more efficient, although he had a distinct feeling of strangeness referable to his eyes. However, as soon as the nystagmus started to reappear, the patient began to show all those disturbances which would be expected to appear if his nystagmus had been acute rather than persistent and chronic (e. g., if it had been due to latent nystagmus or produced by a recent lesion).

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20. Koffka, K.: Principles of Gestalt Psychology, New York, Harcourt, Brace and Company, Inc., 1935.

21. In numerous other cases of congenital nystagmus we were able to obtain the same temporary improvement in visual acuity by injection of sodium amytal. The improvement was both objective (as tested on the Snellen chart) and subjective. Indeed, 1 patient felt so much relieved from his ocular distress when under the action of the drug that he expressed a desire to have an injection "at least once a day."

The once-achieved equilibrium of function was abolished, and the patient's perceptions assumed a point to point relationship to the abnormal retinal patterns. He thus showed the opposite of the constancy effect of the normal person. This effect has been described as an indication of one's ability to depart from such point to point relationships between peripheral stimulus patterns (the proximal stimuli of Koffka), and thus to approximate the "real" object more adequately. (A circle appears as a circle even though it is tilted out of the frontal parallel plane. It is normally not seen as an ellipse, despite the fact that the retinal projection is an ellipse.) It was Thouless [22] who termed these constancy phenomena "regressions to the real object." Disregarding the difficulty of defining the "real" object independently of one's perceptions, we can use an inversion of his term in a merely descriptive manner. Our patient's behavior during recurrence of the nystagmus represents a "regression to the proximal stimulus." [23]

However, this regression to the proximal stimulus was not complete. Objects—even narrow lines—did not move with the slow phase of the nystagmus but appeared broadened or lengthened, depending on their orientation in the vertical or the horizontal dimension of the patient's visual field. Their unitary character as distinct percepts was preserved, except for the episode of diplopia.

Furthermore, the broadening and thinning of vertical lines and the lengthening and shortening of horizontal lines did not follow the rhythm or rate of the nystagmus. The fluctuation was considerably

22. Thouless, R. H.: Phenomenal Regression to the Real Object, Brit. J. Psychol. **21**:339-359, 1931; **22**:1-30, 1931.

23. Regression is to be taken in the spatial sense only, not in the genetic sense. We do not imply that at any time during the development of perceptual organization there actually is a point to point correspondence between proximal stimulation and perception. Likewise, "proximal stimulus," like "real object," is used here as a mere construct because of its illustrative power. The concept of proximal stimuli is obviously an inference from the physiologic theories of sensation. They never exist in a biologic sense for the organism itself, unless and until they are perceived, that is, unless they assume the character of objects. Conversely, real "visual" objects are characterized by their relative constancy of form, size and color, or their comparative independence of the observer's position, of his inner state, and even to some extent of the sense modality which is called into play. It is evident that Thouless' description of constancy phenomena as regressions to real objects involves a logical circle, since phenomenal constancy is the main characteristic of these real objects. However, the converse, or regression to the proximal stimulus, may assume a more biologic meaning, for if, and when, constancy is disturbed, or the framework of one's perception impaired, perceptual phenomena are encountered which approximate such functioning as would have to be expected in terms of physiologic hypotheses about peripheral sensory patterns.

slower and suggested a staggering of the central effect produced by the rapid, repeated shifts of the stimulations on the retina.

The phenomena observed in the Schröder staircase test are of special interest in this connection: There, the lengthening and shortening of the base line were synchronized with the changes in configuration, thus testifying to the unitary character of the percept.

Significantly, no broadening or lengthening of lines was perceived by the patient when he announced his monocular diplopia. This diplopia was the only instance of actual disruption in the formation of perceptual units. It appeared as the extreme disturbance, when compared with the other disturbances in this case (viz., elongation and apparent motion), and it took the place of the latter as soon as it occurred. As the nystagmus became less pronounced, the diplopia disappeared, whereas the lengthening and shortening of lines appeared again.

During the days following the experiment the diplopia did not recur. However, subsequent observations and experiments revealed that the patient's visual organization was influenced by his nystagmus in many more ways than we had originally expected. Some of these phenomena were clearly enhanced and brought to the fore by the injection of sodium amytal, and they thus represented a persistent effect of the brief period of visual disorganization. Others had not been noticed during the preexperimental period, yet seemed to be integral features of the patient's individual "mode" of perceiving.

For instance, there was a consistent tendency to overestimate horizontal, as against vertical, dimensions. Free designs, as well as reproductions of geometric patterns, were characteristically flattened (fig. 3). But, in contrast to the "dramatic" period of recovery from the barbiturate, our patient was not aware of those distortions as such. They belonged to his framework, or to the "silent" organization, in which his perceptions were embedded.[24]

This framework, however, not only was overdetermined (distorted) by abnormal ocular motion but was made deficient by it. In the weeks following the experiment, just as during the period prior to the injection, we found evidence of a large reduction in the phenomena of constancy

24. In a separate publication, further instances of such anisotropy of subjective space (inequality of dimensions of visual space) will be offered. For our patient, it could be shown that the trend toward deformation was always with him. It was abolished only once, under the immediate influence of the barbiturate, when the patient's nystagmus had been arrested. During the follow-up period after the experiment, we succeeded in duplicating this situation by presenting visual stimuli in tachistoscopic exposure. If the speed of exposure became too high for the nystagmus to play any role, the flattening of patterns disappeared. But with a slight variation in the experimental procedure (exposure of objectively "flat" patterns previous to the test—configurations) the latent trend toward distortion was brought out again with any speed of exposure.

of visual objects for size, as well as for form and for color. In that respect, the patient's nystagmus acted like a reduction screen (Katz [25])—the simple cardboard with a hole in the middle, which immediately abolishes the effects of color constancy. Apparently, the nystagmus strips the visual field of the manifold reference points which seem necessary for the obtaining of normal field gradients and constancy effects.

Yet, in spite of the abnormality of the patient's framework, the formation of unitary and unambiguous percepts remained possible, unless the patient was stimulated under highly artificial conditions. Only when a perceptual context as such is missing (as in dreams; in

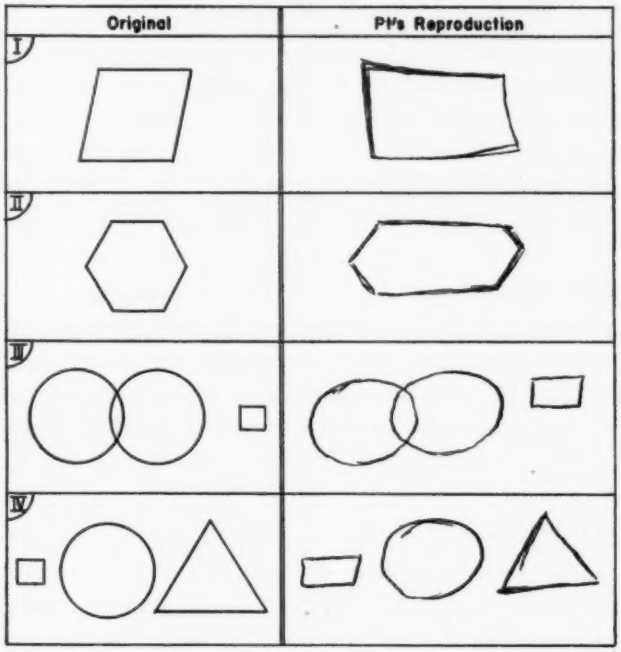

Fig. 3.—Distorted reproductions of patterns from the Benton visual retention test (Benton, A. L.: Visual Retention Test, Arch. Neurol. & Psychiat. **54**:212-216 [Sept.] 1945) made during the period of follow-up study. The patient was not aware that he departed from the original patterns.

free drawings, in which the patient has neither skill nor experience, or in inspection of small figures and lines) do the perceptions follow directly the "pull" of the congenital nystagmus, and only then do the resulting distortions become pronounced enough to be noted by the patient himself. These gross distortions assume three principal forms, which are listed here in decreasing order of degree of disturbance and,

25. Katz, D.: Der Aufbau der Farbwelt, ed. 2, Leipzig, Johann Ambrosius Barth, 1930.

conversely, in increasing order of frequency: (1) double image formation (only episodic, during recovery from sodium amytal); (2) apparent motion of small stationary objects (fairly common with prolonged fixation of two dimensional geometric patterns), and (3) broadening of vertical dimensions and/or lengthening of horizontal dimensions (relatively most common). Among these three forms of deviant percept formation there obtains a relationship of functional equivalence. At any one moment, and in any state of the organism, one, and only one, of these distortions appears in the center of the visual field.

SUMMARY AND CONCLUSIONS

In 2 cases of transient monocular diplopia, ocular movements during fixations were found to play a major role. Whether they actually represent the decisive causal factor in the production of monocular diplopia cannot be established on the basis of the evidence at hand. The possibility cannot be ruled out that both abnormal excursions of the eyes and monocular diplopia are consequences of one and the same central impairment in function. But our observations illustrate the close interrelationships between perception and movement in the building up of the perceptual world.

The ocular movements during fixation impress one as a necessary, but not a sufficient, condition for the development of monocular diplopia. If it were a sufficient condition, one would expect to find monocular diplopia much more frequently in cases of recently acquired nystagmus, as in miner's nystagmus or in other types of acquired nystagmus. In patients who show abnormal ocular movements during fixation, resulting from heteronymous field defects with involvement of the maculas, diplopia is found, but it is apparently limited to binocular vision.

In our 2 cases of monocular diplopia there were additional causal factors which make it understandable why the ocular movements produced such extensive distortions of the patient's perceptions. The diplopia in these cases represented only one phase in the development of a syndrome of visual dysfunction which has been characterized as a disturbance of the dynamic equilibrium of the perceptual organization (including the oculomotor component). The disruption of this equilibrium in and by itself appears as the precipitating factor. It was found in both cases, in case 1 in the form of a cerebral pathologic process and in case 2 as the toxic effect of administration of a barbiturate. In that sense the 2 cases are not complementary but analogous.

Furthermore, the equilibrium in both cases had certain inherent deviant characteristics which made the development of diplopia after disruption of the balance possible. We thus have three levels of causation, which are here summarized in inverse chronologic order.

1. The nystagmoid movements during fixation—a necessary condition for monocular diplopia in these cases.

2. A disruption of the equilibrium of perceptual functions by a toxic or an inflammatory process—the precipitating factor.

3. Finally, in both cases there was the predisposing factor: The equilibrium before its disruption by disease or experiment was different from the equilibrium found in normal persons. In both cases the visual functions had to cope with abnormal conditions of proximal stimulation. In the first case there was congenital convergent strabismus. In the second case there was congenital nystagmus. Neither of these conditions led to diplopia, since they were genuinely congenital. The unitary character of percepts was just as little disturbed as the orientation of one's visual space is influenced by the fact that the lens system gives an inverted picture of the world to the optic tract. However, when, in analogy to Stratton's experiment,[26] the functional organization was disturbed, there were indications that the equilibrium in our cases had been achieved under special handicaps. For in the period following acute disorganization, or at least modification of functional organization, we encountered a partial regression to the (abnormal) proximal stimulus patterns.

Obviously, in these 2 cases the possible range of predisposing factors is not exhausted. At least one further condition must be added to that of convergent strabismus and congenital nystagmus: namely, the abnormal tonic pull in cases with cerebellar and labyrinthine involvement (Goldstein,[14] Bender[1]). But even in the case of pathologic tonus, it is movement, or at least intended movement, of the receptors which accompanies changes in perceptions.

In all these cases generalized changes in perceptions can be found embedding the monocular diplopia. Such systematic changes are of a higher explanatory value than any monosymptomatic examination could reveal. A full understanding of perceptual disturbances seems impossible without an attempt to observe the total organization, with its interrelationship of perception and movement. For that reason, a complete survey of single cases seems preferable to studies of relative frequencies of symptom associations. At present it is difficult to make exact measurements of visual disorder in cases of this kind. But an eventual explanation of the major perceptual disturbances would take one a long way toward an understanding of normal perceptual function.

1192 Park Avenue, New York.

26. Stratton, G. M.: Vision Without Inversion of the Retinal Image, Psychol. Rev. **4**:341-360 and 463-481, 1897.

USE OF CURARE IN OIL IN TREATMENT OF SPASTICITY FOLLOWING INJURY OF THE SPINAL CORD

EDWARD B. SCHLESINGER, M.D.
NEW YORK

WEST,[1] Burman,[2] Bennett [3] and others described the use of preparations of curare in treatment of various syndromes exhibiting spasticity, tremor and rigidity. They found that curare diminished hypertonia, tremor and involuntary movements. The clinical effect, however, was usually transient and therefore of questionable therapeutic value. Denhoff and Bradley,[4] in a group of spastic children, found that the initial period of response to effective doses was characterized by masked facies, head drop and mental confusion. After these unpleasant reactions had worn off, the useful clinical effect became evident. These therapeutic experiments were carried out with aqueous solutions of the drug, used either intravenously or intramuscularly.

In the present study a group of patients showing intense spasticity accompanying injury to the spinal cord were treated with aqueous solutions of curare. Eleven patients with extreme spasticity were chosen from a large group. Of these 11, 9 had complete paraplegia and 2 had demonstrable voluntary function masked by spasticity. These patients were given aqueous solutions of curare intramuscularly every four days. The results were in accordance with the observations of the previous investigators. Excellent relaxation was obtained, but at its peak it was accompanied by blurred vision, diplopia, general weakness and dizziness. The desired effect reached a peak rapidly and subsided in four or five hours, although in several cases a clinical effect was observable up to eighteen hours. The side effects likewise disappeared rapidly and without residual. Because of these side effects, the practical value of the relief was limited, since the patient could not carry out his usual educational and social activities while they lasted.

From New York Neurological Institute and Department of Neurology, Columbia University College of Physicians and Surgeons.

1. West, R.: Curare in Man, Proc. Roy. Soc. Med. **25**:1107-1116 (May) 1932.

2. Burman, M. S.: Clinical Experiences with Some Curare Preparations and Curare Substitutes, J. Pharmacol. & Exper. Therap. **69**:143-148 (June) 1940.

3. Bennett, A. E.: Clinical Investigations with Curare in Organic Neurologic Disorders, Am. J. M. Sc. **202**:102-112 (July) 1941.

4. Denhoff, E., and Bradley, C.: Curare Treatment of Spastic Children: Preliminary Report, New England J. Med. **226**:411-416 (March 12) 1942.

USE OF OILY SUSPENSIONS

The objection to the use of curare, then, lies in its evanescent effect and concomitant side reactions. In this investigation, various menstruums were tried in an attempt to overcome these handicaps. A suspension in peanut oil and white wax U.S.P., similar to that used by Romansky and Rittman,[5] proved most suitable of the preparations tried.

Method of Preparation.—Crystalline *d*-tubocurarine chloride [6] was suspended in a peanut oil—white wax mixture mechanically. The dosage was determined by clinical assay. A 3 per cent suspension of tubocurarine in a mixture of 4 per cent white wax in peanut oil appeared optimal.

This suspension was used routinely every four days with the aforementioned 11 patients. The average dose was 1.25 ± 0.25 cc., given deep in the gluteal muscles. The following cases illustrate the results achieved.

REPORT OF CASES

CASE 1.—A man aged 34 for twelve months had suffered from a traumatic lesion at the second thoracic level of the cord due to a gunshot wound. A laminectomy within forty-eight hours after injury revealed an edematous, discolored spinal cord in continuity. Within three months there was return of crude sensation, and voluntary power was noted in the left foot. Voluntary power increased regularly, and within nine months the patient could move all muscle groups. However, the return of motor control was accompanied by increasing spasticity in flexion. Ulceration of the mesial aspects of both knees, secondary to adductor spasm, supervened. Fibrosis and contracture at the knee joints followed the prolonged spasm (fig. 1). The patient complained bitterly of pain and attempted suicide in depression over the progress of events.

Use of curarine in oil was started, and a dose of 1.25 cc. was arrived at by estimation of the clinical effect. The patient began to note relaxation of spasm in forty-five minutes and maintained it for an average of seventy-two hours (fig. 2*A* and 1*B*). His subjective symptoms disappeared at the same time. He was encouraged to move about freely and to exercise actively. He noted no increase in paresis during his periods of relief from spasticity. Physical therapy was started and vigorously pursued during these periods. The ulcerations of the knee region healed spontaneously with relaxation of adductor spasm. Muscle tone and volume improved. Over a period of two months there was a perceptible decrease in spasticity over and above the effect of the drug.

CASE 2.—A man aged 24 had suffered from a gunshot wound at the first thoracic segment of the spinal cord for ten months. Laminectomy after injury revealed bony fragments compressing the dura, with an edematous, bruised cord. Complete paralysis was followed by rapid, spontaneous improvement over six months, with complete sensory return and about 70 per cent motor recovery. Intense spasticity appeared with voluntary return of function, and at ten months the patient suffered from severe spasticity in flexion with pronounced contractures at the knee joints.

Curarine in oil was administered in increasing doses. A dose of 1 cc. appeared optimal. The duration of effect averaged seventy-eight hours and was not charac-

5. Romansky, M. J., and Rittman, G. E.: Method of Prolonging Action of Penicillin, abstracted, Science **100**:196-198 (Sept.) 1944.

6. The tubocurarine was supplied by E. R. Squibb & Sons, New York.

terized by any toxic signs or symptoms. During periods of relaxation of the spasticity the patient had excellent motor power, limited severely by his contractures at the knee joints. Intensive physical therapy was started with active and passive exercises. The contractures were rapidly reduced, and muscle strength and volume improved perceptibly.

CASE 3.—A man aged 33 had sustained a complete transection of the cord at the fifth thoracic segment as a result of a gunshot wound one year previously. He suffered from severe spasticity, and a mass reflex was induced by the slightest stimulus. Braces could not be fitted because of this condition, nor could the patient be taken out of bed. Fixation of joints became more and more pronounced. Administration of curarine in oil was started and the dosage adjusted at 1.3 cc.

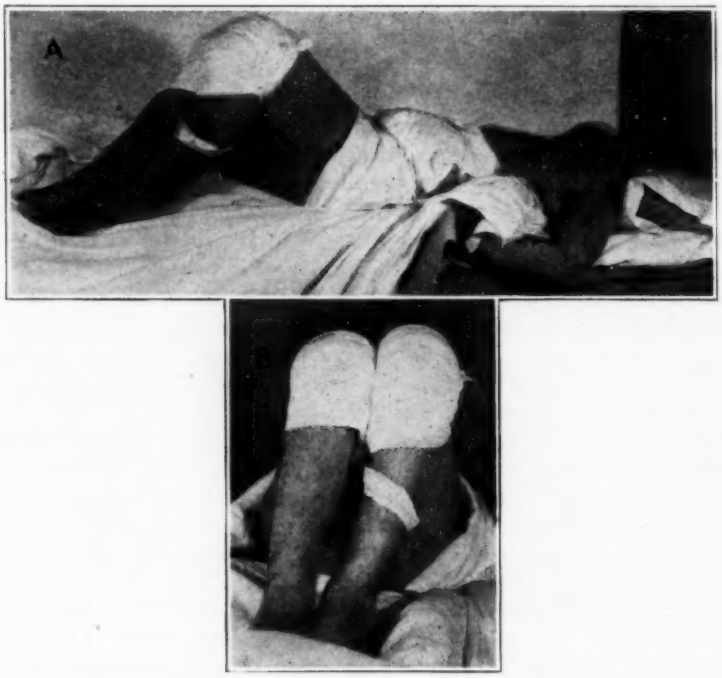

Fig. 1 (case 1).—*A*, position of spasticity in flexion maintained by the patient prior to treatment; *B*, adductor spasm prior to treatment.

The duration of effect was sixty-three hours. During periods of relief physical therapy could be carried out without initiation of mass reflex movements. It was thus possible for the first time to work on the patient's joint fixations and to prepare him for the use of braces later.

CASE 4.—A man aged 24 had sustained a complete transection of the cord at the fourth thoracic segment as a result of a gunshot wound nine months previously. The patient had decubitus ulcers over the trochanteric and sacral regions and on the heels. Healing was prevented by regularly occurring mass movements. Contractures at the knee and the hip joint became pronounced. Physical therapy could not be carried out because of the reactive spasm and the mass reflex movements.

Administration of curarine in oil was started, and 1.5 cc. was found to be the optimal dose. The patient showed clinical relief for periods up to sixty-eight hours. Epithelization was prompt on cessation of the constant friction over the granulating areas. The contractures at the joints were gradually reduced with passive exercises. The patient was helped out of bed to participate in ward activities.

COMMENT

It is noteworthy that none of the undesirable side effects of curare therapy were observed in these cases. During the adjustment of dosage levels occasional slight blurring of vision was noted. At all times the patients were able to carry out their usual activities without handicap. The low levels of curare in the circulating blood probably accounted

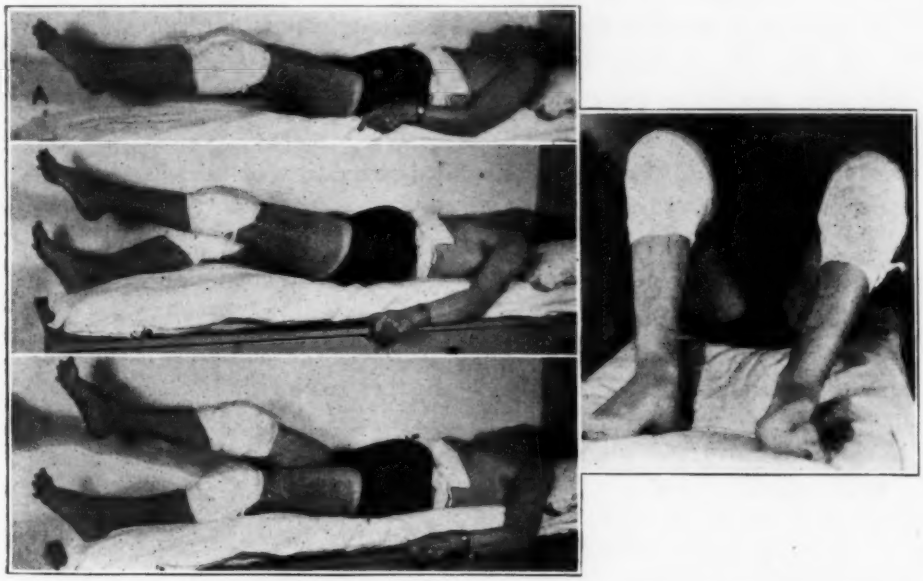

Fig. 2 (case 1).—Patient twenty-four hours after injection of suspension of curarine in oil. *A*, full voluntary extension of the lower extremities, with normal range of motion; *B*, reduction of adductor spasm.

for this phenomenon. Since determination of levels in the blood was not feasible during this study, the exact mechanism of the prolonged effect of curare is not known.

In this small series it was noted that the relaxation was more striking in the paretic than in the paraplegic patients. No explanation of this fact can be given at present.

Continued studies on the clinical use of long-acting preparations of curare are contemplated. Their use in the treatment of other diseases exhibiting spasticity, rigidity and tremor will be the subject of future investigation.

SUMMARY

A suspension of curare in a mixture of peanut oil and white wax afforded good relaxation of muscle spasm of up to three days' duration in a group of patients with injuries of the spinal cord. Effective reduction of spasticity was not accompanied in any case with the usual effects of curare, such as severe changes in accommodation and head drop. Slow absorption, with avoidance of unpleasant side effects, greatly enhances the therapeutic value of the drug.

1. A suspension of *d*-tubocurarine chloride in a peanut oil–white wax mixture yields a slow action curare effect, lasting in some instances up to three days.

2. The action of such a preparation is not characterized by the concomitant appearance of the undesirable side effects of curare.

3. The use of curare in oil in relief of spasticity following injury to the cord seemed of therapeutic value in a series of 11 cases, of which 4 are cited in this paper.

4. The value of drugs which afford relaxation of muscle spasm in permitting physical therapy is stressed.

5. The effect of curare in oil on patients with some voluntary function masked by spasticity seemed more dramatic than the effect seen in paraplegic patients.

6. The effect of curare in oil in treatment of syndromes exhibiting spasticity, tremor or rigidity will be further explored.

Mr. Joe V. Tucker and Mr. Robert Felberg gave technical assistance in this study.

News and Comment

ORGANIZATION OF EASTERN ASSOCIATION OF ELECTROENCEPHALOGRAPHERS

Twenty-seven prominent civilian and military electroencephalographers from several states met at the Graduate Club of the Institute of Living in Hartford, Conn., on March 1, 1946, to organize the Eastern Association of Electroencephalographers. Formed for the purpose of promoting research in the field, the association plans to pool scientific information concerning the neurophysiology and clinical application of electroencephalography.

Lieut. Comdr. Robert S. Schwab (MC), U.S.N., of the United States Naval Hospital in Boston, was elected chairman of the association, and Dr. Charles W. Stephenson, of Hartford, was elected recorder.

One of the immediate projects of the group is to approach the American Physiological Society, the American Neurological Society, the American Psychiatric Association and the Council on Physical Medicine of the American Medical Association on the matter of establishing a joint committee among the several organizations for the purpose of considering the desirability and means of establishing minimum standards for approved electroencephalographic laboratories. Chairman of the committee appointed to pursue this project is Dr. Hallowell Davis, associate professor of physiology at Harvard University; members are Dr. Paul A. Hoefer, associate professor of neurology at Columbia University, and Dr. Margaret Kennard, assistant professor of neuropsychiatry and neuroanatomy at New York University.

Dr. Wladimir T. Liberson, director of the Physiological Research Laboratory at the Institute of Living, Hartford, Conn., and professor at Ecole des Hautes Études, New York, was appointed chairman, and Dr. Leslie F. Nims, assistant professor of physiology, Yale University, and Dr. Margaret B. Rheinberger, who is in charge of the electroencephalographic laboratory at Montefiore Hospital, New York, were appointed members of the organization and program committee.

Attending the meeting were Dr. John A. Abbott, Dr. Mary A. B. Brazier, Dr. Hallowell Davis, Mr. and Mrs. Albert M. Grass, Dr. Milton Greenblatt, Lieut. Comdr. Herbert I. Harris (MC), U.S.N.R., Dr. Hudson Hoagland, Lieut. Comdr. Robert S. Schwab (MC), U.S.N., and Dr. Wolfgang Sulzbach, of Boston; Dr. Pablo Anglas, Dr. Santiago Castillejos, Dr. Wladimir T. Liberson and Dr. Charles W. Stephenson, of Hartford, Conn.; Lieut. Charles E. Henry (MC), U.S.N.R., of Newport, R. I.; Lieut. David G. Jones, M.C., Army of the United States, Lieut. Curtis Marshall (MC), U.S.N.R., and Dr. Charles I. Kaufman, of New London, Conn.; Dr. Milton H. Kibbe, of West Springfield, Mass.; Dr. Margaret Lennox and Dr. Leslie F. Nims, of New Haven, Conn.; Dr. Donald B. Lindsley, of Providence, R. I.; Dr. Abraham Mosovich, of Washington, D. C.; Dr. Paul A. Hoefer and Dr. Margaret B. Rheinberger, of New York; Lieut. Russell Anthony (MC), U.S.N.R., and Comdr. William F. Murphy (MC), U.S.N.R.

The newly formed association will meet bimonthly, with the seminar type of meeting preferred. The second meeting is scheduled to be held at the Graduate Club of the Institute of Living at 1 o'clock on Friday, April 12, 1946, at which time a draft of the constitution and by-laws will be presented by the organization

and program committee. Also, military experiences in electroencephalography will be discussed by Dr. Milton H. Kibbe, who will speak of the Army work, and Dr. Charles B. Henry, who will report on Navy data.

AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY

The spring examinations for certification by the American Board of Psychiatry and Neurology will be held in Chicago on May 23, 24 and 25 at the Illinois Neuropsychiatric Institute. There will also be a one day examination in San Francisco on June 25. Acceptance of applications for these examinations ended March 13.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Psychiatry and Psychopathology

DEPRESSION — THE OEDIPUS CONFLICT IN THE DEVELOPMENT OF DEPRESSIVE MECHANISMS. EDITH JACOBSON, Psychoanalyt. Quart. **12**:541, 1943.

Jacobson reports the results of psychoanalysis in the case of a woman aged 24 who had a depression at 3½ years of age and again at puberty and finally one which brought her for psychoanalysis. Her father suffered from severe depressions. Jacobson places her condition in the manic-depressive group, but it was difficult to decide whether it might not be a severe anxiety hysteria with borderline depressions. Analysis showed that at the age of 3 there was the beginning of a normal Oedipus situation. In the next half-year she suffered a series of traumatic incidents, among which was contact with her father's penis, which aroused her genital sensations intensely and prematurely and led her to expect a gratification from him similar to the gratification which she obtained from the frequent enemas given by her mother. She also had a frightening experience with a psychotic maid and recalled her mother's pregnancy with her brother. This series of traumatic incidents ended in a psychic collapse at the age of 3½ years. As a result of these incidents she felt disappointed by her father, and in bitter hate she turned away from him and back to her mother. Here, again, she was disappointed because the mother loved only the baby. In her disappointment and hostility she tried to escape into a narcissistic withdrawal and kill her need for love by becoming absolutely self sufficient and independent. In this goal she failed because of her intense ambivalence, as it was expressed in her fantasies of the primal scene—her wishes for participation in the sadistic fight of her parents and for their incorporation and annihilation. In vain she attempted to ward off her destructive impulses by identifying herself with the image of her good parents and by rebuilding her love relationship to them. The outcome of this conflict was her first depressive collapse. From that time she shifted her ambivalent desires from one parent to the other, without being able to establish a firm relationship with either. In her most balanced periods she found some security in her dependent but reliable bondage to her mother, competing with her brother by being the oversubmissive child. She invited her father's appreciation by her intellectual superiority.

This aggressive desertion of one parent for the other, with its guilty reactive sadomasochistic love, seems to be typical of the Oedipus situation in cases of the manic-depressive psychosis.

After disappointment in the homosexual object the patient breaks away aggressively and approaches a heterosexual object. Unable to carry out this attachment because of ambivalence, he vainly attempts to return to the homosexual object. This attempt fails because of ambivalence. Then the patient goes into a depression.

PEARSON, Philadelphia.

INVESTIGATION AND TREATMENT OF ENURESIS IN THE ARMY: PRELIMINARY REPORT ON 277 CASES. P. L. BACKUS and G. S. MANSELL, Brit. M. J. **2**:462 (Oct. 7) 1944.

Backus and Mansell made a study of the results of treatment of 277 unselected patients with nocturnal enuresis consecutively admitted to a military hospital during a period of eight months. A complete routine physical examination revealed no abnormality in 92.06 per cent of the patients. A cystometric examination was performed on 232 patients. The ages ranged from 14 to 45, with an average of 21.33 years. The intelligence rate, based on the matrix test, ranged from S. G. I

to V, with a mean of S. G. III plus. A history of nocturnal enuresis from infancy was elicited from 75.81 per cent of the patients. From the psychiatric study, the men were classified under six personality types: timid, 48.01 per cent; average, 27.07 per cent; compensatory aggressive, 10.49 per cent; purely aggressive, 6.14 per cent; psychopathic, 5.77 per cent, and predominantly obsessional, 2.52 per cent. It was noted that the older the patient and the poorer the intelligence, the greater the difficulties in treatment. Follow-up observations on 40 patients in the series showed that 31 were returned to full duty with satisfactory bladder control and 4 to light duty with satisfactory bladder control; 2 were discharged, and 3 were readmitted for further treatment. The authors concluded that suitability of such patients for treatment in the army is dependent on the following factors: the age, preferably under 30; fair intelligence; bladder capacity of more than 300 cc. and water pressure of 60 cm., and evidence of voluntary powers of relaxation.

ECHOLS, New Orleans.

Meninges and Blood Vessels

TUBERCULOUS MENINGITIS: REPORT OF A CASE WITH CLINICAL RECOVERY. DOMINGO UNCHALO, Rev. med. d. Hosp. ital. de La Plata **1**:39 (Oct.-Dec.) 1944.

Unchalo presents a case of recovery from tuberculous meningitis three years after the illness. The man was 28 years of age at the beginning of his acute illness, on Nov. 26, 1941. The clinical picture was that of acute meningitis, with 96 cells in the clear, but mildly xanthochromic, spinal fluid. There were 68 per cent lymphocytes and 32 per cent polymorphonuclear leukocytes. The sugar of the spinal fluid measured 38 mg. and the chlorides 500 mg. per hundred cubic centimeters. Five tubercle bacilli were found in the centrifuged spinal fluid. No cultures or animal inoculations were made. The reaction was positive to tuberculin. A roentgenogram of the chest showed old sclerotic and calcified lesions. The patient was treated with intrathecal injections of gold salts. The author believes that his patient had tuberculous meningitis.

SAVITSKY, New York.

Diseases of the Brain

POSTCONTUSIONAL HEADACHE. ERICH GUTTMANN, Lancet **1**:10 (Jan. 2) 1943.

Little is known of the factors which lead to the development and persistence of the common after-effects of head injury (headache, giddiness and lack of concentration) in some persons and not in others. Guttmann reports on 200 patients representing consecutive admissions for head injury for whom the presence or absence of headache was noted in the records.

The duration of post-traumatic amnesia, assessed at the time of discharge from the hospital, was used as an indicator of the severity of the injury. For 179 of the patients the data were as follows:

	Duration of Post-Traumatic Amnesia	No. of Patients
Group O	5 min.	33
Group A	1 hr.	85
Group B	24 hrs.	39
Group C	7 days	19
Group D	Over 7 days	3

Less than one-half the patients complained of headache when they awoke from unconsciousness, and the proportion grew smaller the longer the unconsciousness lasted. This may be due to the inability of patients with severe injury to observe and describe their sensations. Of 166 of these patients, 76 complained of headache (mild or severe) at one time or another during their stay in the hospital. Only 154 were examined at the time of discharge, and of these, 32 had headache. At a time when it was expected that the patients would be fit for work again, 38 per cent

of them had headache. At the end of three months only the patients who had returned to work were examined, and here, again, the incidence of headache was 21 per cent. Six months after the injury it was 18 per cent.

Up to and including the time of the first follow-up examination, the incidence of headache among patients with milder injury was persistently higher than that among patients with severe injury. Three to six months later this difference disappeared. This observation seems to point to factors not immediately connected with the mechanical injury. If the duration of the post-traumatic amnesia is a rough measure of the severity of injury, one would expect some correlation between symptoms and severity independent of the lesion in a given case. The 23 patients who had headache six months after injury were examined clinically, in the hope of shedding light on this question.

In this group of 23 patients age was not considered an important factor. Roughly, 25 per cent were under 20 years of age; 25 per cent were over 50, and the rest were between 21 and 50 years old. One patient was excluded because the presence of acute otitis media explained his headaches. Six patients revealed that they had had similar headaches all their lives. Two patients reported cessation of their headaches during the time of observation. One patient, an elderly spinster, had received medical care for years for nervous exhaustion. Another patient, a nervous child, never complained of headache which an overprotective mother insisted was present. Another patient was a defective, emotionally unstable girl, who had had variable nervous symptoms all her life. Nine patients presented fairly obvious psychogenic motivation. Guttmann points out that this does not exclude an organic basis, but that since most patients with similar injuries do not complain of headache, it is fair to assume that either the symptom itself or the patient's attitude toward it is determined by demonstrable psychologic factors rather than by the hypothetic organic basis. In only 2 cases of the group was no cause for the persistent headache discovered.

It seems possible, with active treatment, to discharge 80 per cent of patients from the hospitals free of complaints. Less than one-half the patients discharged are left with some liability to headache. This predisposition is psychosomatic; that is, psychologic factors are as important as physical factors in precipitating headache. It is the opinion of the author that they are more important.

SANDERS, Philadelphia.

SULPHANILAMIDE POISONING WITH CEREBRAL MANIFESTATIONS. HOWARD REED, Lancet **2**:535 (Oct. 21) 1944.

Reed describes the case of a 3 year old girl who took sulfanilamide by mouth when left alone for three hours. She was found unconscious and stiff in hyperextension, with the right arm flexed. She alternated between quiet and excited periods, with grotesque convulsive movements or thrashing from side to side, during the first twelve hours. She then was able to recognize a friend and improved slowly but steadily during the next several days.

Reed compares the dilated pupils, teeth grinding, rigidity and convulsive movements seen in this girl with the same signs found by Hawking in rabbits and cats after similar doses of a sulfonamide compound (*Lancet* **2**:1019, 1937). This child's restlessness was also similar to that seen in a case of overdosage of a sulfonamide drug reported by Cutts and Bowman (*New England J. Med.* **225**:448, 1941).

MCCARTER, Boston.

QUININE BLINDNESS. I. S. MCGREGOR and ARNOLD LOEWENSTEIN, Lancet **2**:566 (Oct. 28) 1944.

McGregor and Loewenstein describe the case of a man aged 37 who had had malaria twelve years previously and had been treated with quinine, with no trouble other than transient tinnitus and deafness. He was given 30 grains (1.95 Gm.) of quinine dihydrochloride every two hours for a recrudescence of fever. In thirty-

six hours he was blind and deaf; the deafness cleared quickly, but the amaurosis improved only slightly. The retinas were milky in appearance, and there was a cherry red spot at each macula. Treatment was with purgation with magnesium sulfate, protein shock and forced fluids and dextrose. After several days administration of a preparation of vitamin B complex and ascorbic acid was added. The retinal arterioles became narrow and the optic disks rather pale. The pupils reacted slightly to light, but colors could be recognized on Ishihara plates, though the patient could not read numbers two or three weeks after onset. The visual fields were carefully tested and found to be constricted, but not so much so as the responses would indicate. It was found that they were sievelike, in that several scotomas deprived them of uniform perceptual quality. Visual acuity was 6/60 in the right eye and 6/5 in the left eye. Several months later the patient had learned to use his vision more skilfully (visual acuity 6/12 in the right eye and 6/24 in the left eye), but for practical purposes he was blind.

The authors attribute the milky appearance of the retina to ischemia caused by thromboses, due, in turn, to toxic proliferative changes in the arteriolar endothelium. Quinine also acts on the ganglion cells.

The authors urge prevention by careful use of quinine, not more than 30 grains (1.95 Gm.) daily, and not this much until administration of small doses has ruled out sensitivity. When blindness has occurred, therapy aims to effect early and vigorous exchange of fluid. Locally, paracentesis of at least one eye was tried in this case, and the procedure is advised in addition to general methods. Vitamins are used to facilitate oxygenation in the retina.

McCarter, Boston.

Significance of the Pupillary Light Reflex in Diseases of the Nervous System. J. Candido da Silva, Arq. de neuro-psiquiat., São Paulo **1**:271 (Dec.) 1943.

In 1753 Robert Whytt first showed that the pupillary reaction to light is a true reflex. The author insists that an Argyll Robertson pupil is always bilateral. The pupils are considered miotic when they are less than 2 mm. in diameter. He found the Argyll Robertson pupil in only 7 of 300 patients with dementia paralytica. The presence of this pupil in cases of this disease indicates a poor prognosis. Six of the 7 patients died, and 1 failed to respond to treatment. In 2 patients pathologic responses to light occurred as an isolated symptom, without evidence of syphilis or any other disease. The author emphasizes the inadvisability of using the term Argyll Robertson pupil indiscriminately.

Savitsky, New York.

Neuropsychiatric Aspects of Manganese Intoxication. Isaac Horvitz and Enrique Uiberall, Rev. neurol. de Buenos Aires **9**:1 (Jan.-March) 1944.

Horvitz and Uiberall report neuropsychiatric changes in 64 cases of manganese poisoning among workers in manganese mines in the north of Chile. The patients, from a group of 800 workers, were observed over a period of three years; 39 were examined personally. The manganese, from manganese oxide, readily becomes pulverized and was found in the atmosphere of the mines in concentrations as high as 250 mg. per cubic meter. The time of exposure to the manganese before symptoms appeared varied from forty-nine to four hundred and eighty days, with an average of one hundred and seventy-eight days.

Five of the personally observed patients had a prodromal period, with headache, weakness, pain in the muscles, sialorrhea and somnolence. Seventeen of the other 34 patients had definite mental changes; 12 had neurologic signs and 5 did not. Fourteen had a relatively benign manic syndrome; the other 3 exhibited manic excitement with irritability. Mental symptoms occurred in 34 of the 64 patients. The most characteristic mental change was a manic syndrome with elation and a peculiar impulse to sing, run, dance and work at a rapid pace. There was no confusion or evidence of intellectual enfeeblement during the acute psychosis; all the patients showed insight into their morbid behavior. Three patients had

visual hallucinations (zoopsia), which were terrifying in only 1 case; all the patients had amnesia for the episode. The manic syndrome showed less pronounced elation, less flight of ideas and definitely less bizarre mental content than the classic manic psychosis. Only 1 patient, during the height of the illness, showed some aggressiveness, with antisocial tendencies. These episodes lasted from ten to twenty days in most cases, and never longer than seven weeks. Persistent mental changes were rare but did occur. The authors note that persistent enfeeblement and euphoria were present one and one-half years after the acute psychosis in 1 patient. Another had recurring fugue reactions for six months.

Forty-one of the 64 patients showed definite neurologic changes. In the patients with concomitant mental changes, the neurologic manifestations usually appeared a few weeks to three months after the mental symptoms. In only 1 patient did mental changes appear one month after the neurologic symptoms. All the patients showed involvement of the extrapyramidal system. Eighteen patients exhibited concomitant signs referable to the pyramidal tract. The clinical picture was that of paralysis agitans. Hypokinetic phenomena predominated; 1 patient exhibited choreiform movements and 2 tremors. Paresis of convergence was noted twice and defective pupillary contractions during accommodation once. Perioral tremors with voluntary movements were observed in 3 patients and constant hyperexcitability of the facial muscles in 3 others. Sensory changes were noted in 7 patients, involving the whole body in 2; they were not of an organic pattern. The course of paralysis agitans was much more rapid after manganese poisoning than after encephalitis; there was no long interval of freedom after exposure to the manganese. Most of the patients showed progression toward a definite picture of paralysis agitans, but the condition of some did not progress. Actual regression, though rare, was observed.

SAVITSKY, New York.

Diseases of the Spinal Cord

THE DIAGNOSIS OF POSTERIOR HERNIATION OF THE LUMBAR INTERVERTEBRAL DISKS. DONALD MUNRO, New England J. Med. **232**:149 (Feb. 8) 1945.

Munro presents data on two parallel series of cases in which the history and the results of physical examination might generally be considered to justify a diagnosis of herniation of the nucleus pulposus from a ruptured lumbar intervertebral disk. In one series, of 28 cases, a herniation was proved to have been present by operation and by examination of the removed material in all but 3 cases, in which unmistakable and characteristic myelographic deformities were present. In the other series, of 41 cases, the following diagnoses were made: ruptured intervertebral disk, 13 cases (proved wrong by operation in 10); compression of a nerve root by a small dural envelope or local scar resulting from a fractured lumbar vertebra, 19 cases (in 14 of which the diagnosis was verified by operation); questionable radiculitis, the cause of which was not apparent, 4 cases (verified by operation in all); congenital defect without other demonstrable disease, 2 cases (verified by operation in both), and strained back, 3 cases (verified by operation in 1). Of 9 of the cases in which the clinical diagnosis was not verified by operation, an abdominal aortic aneurysm was visible roentgenographically in 1. The myelographic evidence was negative for the lesion in this case. In 1 case four myelograms were negative; an operation was not performed in spite of a "typical history." In 1 case there was an unquestionably positive myelogram, and operation was advised but refused. In 5 cases herniated disks had previously been removed elsewhere, only to have the symptoms recur in four to eleven months. In 2 of these cases the myelogram was abnormal but not characteristic of herniation, and in 1 case it was normal. All 5 patients are awaiting a second operation. In the last (ninth) case the history and physical examination suggest a herniated disk and the myelographic evidence is questionable, but the patient has refused operation.

From an analysis of these data, Munro concludes that a clinical history and an examination that even includes a study of the cerebrospinal fluid are not enough

to justify an indisputable diagnosis of posterior herniation of a lumbar disk. An unequivocal recommendation of operation as a method of treatment is equally unjustifiable in such circumstances. If, however, one can demonstrate a sensory deficit that corresponds to the peripheral distribution of a low lumbar or an upper sacral root, together with atrophy and loss of the ankle jerk in the same leg, a diagnosis of irritation or compression of the particular root is justified.

If, in addition, there is a history of intermittent attacks of pain in the back with radiation to any part of the leg, especially to the lower portion, which is associated with initiation or increase of the typical pain by coughing, sneezing or straining or by motion of the back or lifting, and if these attacks started after an injury to or strain of the back, a lifting strain or a fall, a posterior herniation of either the fourth lumbar or the lumbosacral disk must be seriously considered as a cause of radiculitis. This cannot be regarded as approaching a certainty, however, unless confirmed by other, and more accurate, data. Additional symptoms and signs, whether present or absent, neither strengthen nor weaken this possibility. A positive straight leg–raising or Lasègue test, limitation or loss of motion of the back, a change in the lumbar curve, spasm of the erector spinae muscles and local tenderness in the lumbosacral area indicate only that the patient has some trouble with the lower part of his back, the lumbosacral roots or the cauda equina and neither confirm nor deny the diagnosis of herniation.

A history and examination such as that previously given, if accompanied with partial or complete dynamic block or with an increase in the total protein content of a sample of cerebrospinal fluid properly collected from below the level of the block or with both, justify a diagnosis of irritation or compression of any part or all of the cauda equina and a probable diagnosis of either an intraspinal tumor or a midline posterior herniation of a lumbar disk. Final differentiation must at least await myelographic study, and in many cases operation.

The level of herniation, if one is present, is usually not determinable on the basis of clinical data alone, and it is entirely out of the question to diagnose and to localize multiple herniations without adequate preoperative visualization of the lower subarachnoid space.

Certain diagnosis, concerning both the presence of a herniation or herniations and the level, depends on adequate visualization of the lumbosacral subarachnoid space by an opaque contrast medium. So far, a 20 per cent solution of skiodan has proved satisfactory for this purpose.

Clinical examinations lay the groundwork for suspecting the presence of posterior herniation of a lumbar disk. Myelographic examination with a contrast medium proves or disproves its presence, determines the level of the herniation and leads to a minimal amount of surgical intervention should this be indicated.

GUTTMAN, Philadelphia.

Peripheral and Cranial Nerves

PRESSURE PALSY IN THE PARALYSED LIMB. W. LEWIN, Lancet **2**:756 (Dec. 18) 1943.

Lewin reports 5 cases of popliteal nerve palsies in patients with traumatic injuries of the brain and cord. The clinical separation of the peripheral nerve injury from the disease of the central nervous system is often difficult or impossible. Clinical examination shows, theoretically, a sensory loss over the distribution of the affected nerve and a flaccid paralysis, as against a spastic paralysis of the surrounding muscles. There would be a "continued absence of power in the peroneal and anterior tibial muscle groups of a limb otherwise recovering; a disproportionate rate of wasting of these muscles in the paralyzed limb; failure of these muscles to participate in the mass reflex in a case of paraplegia; failure to elicit this reflex by stimulating the dorsum of the foot or outer side of the leg. The presence of a plaster sore or bed-sore over the head of the fibula . . . is always highly suggestive." But one cannot dogmatize on clinical evidence alone; so electromyo-

graphic studies are made. Lewin feels that the "presence of fibrillation action potentials is evidence of a lower motor neurone denervation of the muscles concerned; it does not occur in an upper motor neurone lesion."

The sweating test was quinizarin (1,4-dihydroxyanthraquinone) was also employed to show absence of peripheral innervation. This is particularly helpful in cases of lesions of the cauda equina, in which the sweat fibers have already left the cord and are now distributed with the peripheral nerves. Of the two tests, the sweating test was the chief diagnostic aid; in 4 of the 5 cases it was more helpful than the electromyogram.

Since most of the patients are transported in war areas, under conditions which do not allow optimum care, the author suggests the application of a cotton pad over the lateral aspect of the knee of the paralyzed leg. McCarter, Boston.

Treatment, Neurosurgery

Part-Time Protective Environment and Working Parole as an Adjuvant in the Treatment of Alcoholism. Joseph Thimann, New England J. Med. **231**:9 (July 6) 1944.

Thimann reports the case histories of 3 patients who were addicted to alcohol. These patients were subjected to the so-called conditioned reflex method of treatment and to a plan whereby they were able to work but remained as boarders in an institution. The author stresses the beneficial role of a part time protective environment, which should be continued for about a year, as an adjuvant in the treatment of addiction to alcohol. This plan should be supplemented with the conditioned reflex treatment, psychotherapy, social adjustments and physical therapy.

Guttman, Philadelphia.

Shock Therapy in the Involutional and Manic-Depressive Psychoses. J. A. Bianchi and C. J. Chiarello, Psychiatric Quart. **18**:118 (Jan.) 1944.

Bianchi and Chiarello treated 87 patients with involutional melancholia and 134 patients with manic-depressive psychoses with metrazol and electric shock. Metrazol was used in treatment of the majority of both types of patients. Sodium citrate in large doses was given to prevent thrombosis and to shorten the initial clonic phase, in which it was noted the complications of fracture occurred. A series of fifteen to twenty convulsions were induced, either with the drug or with the electric current.

Of the patients with involutional psychoses, 58.6 per cent left the hospital improved. Of those who did not recover, 75 per cent were of the paranoid type. The patients with involutional melancholia whose symptoms had existed for less than two years did better with shock treatment than those who had been sick longer, but duration of symptoms had only a slight effect on the results for the patients with manic-depressive psychosis. Of the latter, the depressed patients did better than the manic patients. Of both the patients with involutional melancholia and the patients with manic-depressive psychosis who left the hospital after treatment, 90 per cent did so in two months or less.

The only complications of therapy included fracture of the humerus, in 4 patients, and abscess of the lung in 2 patients, the latter occurring before sodium citrate was used with metrazol. These 6 patients were not included in the series, since their treatment was not completed. Two patients with crush fracture of the vertebrae were included, since their fractures were not discovered until routine examination at the end of the course of treatment.

McCarter, Boston.

Effect of Pethidine [Demerol] on Pain in Neurological Cases. Gerald Fitzgerald and Brian McArdle, Lancet **1**:296 (March 6) 1943.

Pethidine, the hydrochloride of the ethyl ester of 1-methyl-4-phenyl piperidine 4-carboxylic acid, was given to 12 selected subjects with severe pain arising from

various neurologic conditions. The pain was: (1) of central origin, (2) of peripheral origin or (3) operative and postoperative. The drug was given by the oral, the subcutaneous or the intravenous route. The dose varied from 50 to 100 mg. Intravenous injections were given slowly, over a period of two to four minutes. The effects were judged by the patient's comments and by clinical observations.

Ten of the patients received the drug intravenously—100 mg. being given to 8 patients, 66 mg. to 1 patient and 150 mg. to 1 patient. Four patients were given the drug subcutaneously—100 mg. being administered to 3 patients and 50 mg. to 1 patient. Four patients received the drug orally—3 having 50 mg. and 1 100 mg. All but 1 patient, who suffered from a painful phantom limb, experienced some degree of relief from pain. In 8 patients the response was excellent. Complete relief from severe pain was obtained for a number of hours. With 1 patient the result was striking. In a child of 12 years a severe headache developed during an encephalographic examination; the pain was quickly relieved by intravenous injection of 66 mg. of the drug, and the rest of the procedure was carried through without discomfort. In 3 of the 12 patients relief was considerable; but pain was not entirely abolished, and the duration of relief was not more than four hours.

Giddiness, faintness, sweating, blurring of vision, nausea, tremulousness and anxiety were the various side effects occurring among 7 of the 10 patients given the drug intravenously. These features were transitory in all but 2 patients, in whom they persisted for fifteen and thirty-five minutes, respectively.

The relief gained with Pethidine was compared with that following administration of ¼ grain (16 mg.) of morphine to 7 patients. All received considerable relief from the drug, but it was less definite and of shorter duration than that following administration of Pethidine.

SANDERS, Philadelphia.

PNEUMOCOCCAL MENINGITIS TREATED WITH PENICILLIN. H. CAIRNS, E. S. DUTHRIE, W. S. LEWIN and H. V. SMITH, Lancet **1**:655 (May 20) 1944.

The authors report on a series of 11 patients with pneumococcic meningitis treated with penicillin. Of these, 3 were moribund and soon died, and the cases are not discussed here. Of 8 patients receiving full treatment, 2 eventually died of diffuse purulent pachymeningitis and cerebral abscess. Sodium and calcium salts of penicillin were used in daily doses averaging 3,000 to 4,000 units per injection but ranging from 10,000 to 85,000 units for total doses over periods of four to nine days.

Penicillin was injected into the lateral ventricle or into the lumbar subarachnoid space or into both. Cisternal puncture was not used either because there was free flow between the lumbar area and the ventricles or because, in 2 cases of block, "it would not have helped." The drug was given in 3 cases by intramuscular injection as well, and "satisfactory blood levels were established."

Twenty-four hours after injection of 3,000 to 4,000 units the concentration of penicillin in the cerebrospinal fluid "was usually about 0.4 unit per cc.—at least ten times that required to produce complete inhibition of the growth of a sensitive pneumococcus." The authors believe that the best way to achieve optimum concentration of penicillin throughout the cerebrospinal fluid is to give it simultaneously by the lumbar and the ventricular route.

Reaction to injection was severe in only 1 case, in which a strong solution of sodium penicillin was used. A mild reaction was "occasionally observed immediately after ventricular injection. It consisted of patchy erythema of the skin of the trunk and limbs, often coming and going, generalised sweating, intermittent goose-skin, slight rise of pulse rate, and sometimes vomiting, the whole passing off in 10 to 20 minutes." The patient with the severe reaction showed the picture just described and then had a large bowel movement on the operating table. She became drowsy, confused and hemiparetic (with residual palatal palsy and dysphagia for two months). Often patients complained of sacral and sciatic momentary pain during the course of lumbar injection.

MCCARTER, Boston.

Society Transactions

PHILADELPHIA NEUROLOGICAL SOCIETY

George D. Gammon, M.D., *Presiding*

Regular Meeting, March 23, 1945

Incidence, Clinical Characteristics and Restitution of War Injuries of Peripheral Nerves. LIEUT. MARTIN G. NETSKY, Medical Corps, Army of the United States.

The peripheral nerves were involved much more frequently in the second world war than in the first (18 vs. 2 per cent). Injury to the radial nerve is commonest in civilian life; in military experience, injuries to the ulnar nerve are commonest (each 25 per cent), and next in frequency are injuries to the radial, median and peroneal nerves (each about 16 per cent). One fourth of all patients have injuries of more than one nerve. Variations in the degree of motor overlap of the median and ulnar nerves are often puzzling. The mechanism of the flexion position of the last two fingers in ulnar paralysis is still an unsolved problem. Prevention of ulcers of the sole of the foot with tibial paralysis is an important problem in enabling patients to work. A new method for the determination of the site of lesions of the brachial plexus was mentioned. Sympathetic block has been found of diagnostic and therapeutic value in the treatment of burning pain. The diagnosis of true causalgia has rarely been made. Almost one third of peripheral nerve injuries recovered spontaneously.

DISCUSSION

DR. GEORGE D. GAMMON: Does Dr. Netsky know any reason that causalgia is less common now than previously?

DR. MARTIN G. NETSKY: There is no reason that I know of. After the Civil War and World War I there were men who were reduced to emotional hulks, but such patients have not been seen at Cushing General Hospital.

DR. MICHAEL SCOTT: Has Dr. Netsky observed any results from nerve grafts?

DR. MARTIN G. NETSKY: Yes, nerve grafting has been done at Cushing General Hospital. It has been employed in a comparatively small number of cases, and for that reason I omitted mentioning it. The results on the whole have not been successful. In 2 of a small number of cases signs of regeneration were shown. In the majority of cases the condition has not improved, and the problem is yet to be solved.

DR. JOSEPH C. YASKIN: I wonder whether Dr. Netsky could inform us regarding the interruption or compression of nerves after operation. Has anything new been learned since 1917-1919 in evaluating the anatomic changes of injured nerves prior to operation? In civilian practice this subject has been, and still is, a major question extremely difficult to answer. It is true that the surgeon operates, but the clinical neurologist often has to determine the advisability of surgical intervention.

DR. MARTIN G. NETSKY: Handling depends on the site of injury. With large gaps the ends are approximated when it is anatomically possible, as in the ulnar nerve. Results with transposition of the ulnar nerve in cases of acute flexion of the arm have been fairly good. In some cases, as in those of lesions of the median nerve in the palm, the procedure is not possible, and grafting is the only resort. In a few cases bone shortening has been done.

In answer to Dr. Yaskin's question: I think there are no new developments in preoperative estimation of the anatomic state of the nerve.

COMDR. WILLIAM GERMAN (MC), U.S.N.R.: I do not believe that any great advance has been made since World War I.

Surgeons have learned to use fine steel and some other forms of suturing material, such as a cobweb-like substance called tantalum. I should be interested to hear what Dr. Netsky and Dr. Lewey have to say about these materials.

Plasma glue is being used, of course, and its proponents will have to speak for it. The chief problem now is the same as it was in the first world war—the approximation of the nerve ends. This may necessitate the shortening of the extremity by bone sections. Many times it means transposition and suturing of the nerve ends, with avoidance of the use of grafts whenever possible.

Management of War Injuries of Peripheral Nerves. MAJOR F. H. LEWEY, Medical Corps, Army of the United States.

I am strongly in favor of the closest possible cooperation of neurologist and neurosurgeon, although the present setup in the Army may require an administrative separation. All patients, whether "neurologic" or "neurosurgical," are admitted to the neurologic section, where they are examined and their cases completely worked up within one week. They are presented to a combined conference of the neurologic, neurosurgical, orthopedic, medical and general and plastic surgical sections. This conference has proved stimulating to all sections, and a great time saver to patients and medical officers alike. In the neurologic examination, those methods are favored which give a permanent and numerical record, permitting comparison of objective data on the return of muscle power and of touch and pain sensitivity. None of the methods of electrical examination so far available has given useful information on the actual condition of a nerve (bruise, functional or anatomic interruption). Patients who require neurosurgical treatment are transferred to the neurosurgical section for operation and returned to the neurologic section for further observation, after-treatment and disposition. New methods have been devised to shorten the time of mobilization of "frozen joints" ("joint bulldozer") and of waiting for the success of nerve sutures (action currents across the suture line) and for the final result (extended work furlough).

DISCUSSION

DR. JOSEPH C. YASKIN: It appears that technical preoperative determination of anatomic interpretation of the nerve has not advanced since World War I.

Dr. Lewey lays less stress on the electrical studies, which received so much attention, especially in Frank's school, in 1917 and 1919. Are Dr. Lewey's procedures applicable in all cases except in those in which operation has been performed? Is there a closed method of evaluating the syndrome of regeneration? In other words, is there a way of telling the condition of the nerve without operation? Is the rate of recovery after operation considerable, and are there failures?

Lastly, Dr. Lewey's anticipation of the care of these patients from the industrial standpoint is very wise; it is a view previously neglected.

DR. CHARLES RUPP: Is Dr. Lewey able to give any data on the average time required for function to return after compression neuritis? What is the maximum period before spontaneous improvement has been noted?

George D. Gammon, M.D., *Presiding*

Regular Meeting, April 27, 1945

Nontuberculous Meningitis in Children: Report on Ninety-Five Cases. DR. J. ALBRIGHT JONES, Swarthmore, Pa.

During the six year period from 1939 to 1944, inclusive, 146 children with nontuberculous meningitis were admitted to the Children's Hospital of Philadelphia and to the pediatric ward of the Philadelphia General Hospital.

Of the 146 patients, 96 had meningococcic meningitis; 20, influenzal meningitis; 19, pneumococcic meningitis, and 9, streptococcic meningitis (2 children with meningitis due to Escherichia coli were not included because they have been reported on before this society by Dr. Gammon).

The mortality percentages were as follows: meningococcic meningitis, 9.3; influenzal meningitis, 65; pneumococcic meningitis, 95, and streptococcic meningitis, 55.

Of the patients with meningococcic type, the records showed petechiae in 20 per cent; the meningococcus was reported in blood cultures in 19 per cent, in spinal fluid cultures in 64 per cent and in smears of the spinal fluid in 73 per cent.

Among the 14 patients with influenzal meningitis at the Children's Hospital there were 9 deaths (mortality, 64 per cent). Among the 6 patients at the Philadelphia General Hospital there were 2 deaths (mortality, 40 per cent). Of the 20 patients, Hemophilus influenzae was found in smears of the spinal fluid in 80 per cent, in spinal fluid cultures in 70 per cent and in blood cultures in 30 per cent.

Laboratory data on the 9 patients with streptococcic meningitis were as follows: Streptococci were found in spinal fluid smears in 62 per cent, in spinal fluid cultures in 100 per cent and in blood cultures in 25 per cent (2 patients did not have blood cultures made).

All but 1 of the 18 children with pneumococcic meningitis died (94 per cent mortality). Pneumococci were found in spinal fluid smears in 88 per cent, in spinal fluid cultures in 94 per cent and in blood cultures in 22 per cent.

With the exception of the patients with meningococcic meningitis at Philadelphia General Hospital in 1944 who were treated with sulfamerazine, not enough patients were treated with any single drug to warrant conclusions regarding the efficacy of a single type of therapy. However, from the reports cited, it seems certain that at present the following statements can be safely made: Sulfadiazine, sulfamerazine and penicillin are all effective agents in the treatment of meningococcic meningitis. Serum is rarely beneficial. Sulfadiazine and anti-influenzal rabbit serum form the best combination for treating infections with type B H. influenzae. Sulfadiazine or sulfamerazine with penicillin probably forms the most effectual combination in the treatment of pneumococcic meningitis. Surgical drainage is worthy of more study. The use of penicillin and a sulfonamide compound for this type of meningitis has been recently reported as an improved therapeutic measure. Streptococcic meningitis should be treated with the same combination as is used for pneumococcic meningitis. Foci of infection in pneumococcic and streptococcic meningitis must be thoroughly cleaned up.

Early diagnosis must be stressed. Parents can help by being "meningitis conscious" during epidemics of meningococcic meningitis. More thorough laboratory work in identification of the causative organism is needed. Much can be accomplished by the intern who makes the first spinal puncture.

Further consideration of surgical drainage in cases of pneumococcic meningitis is needed. Adequate treatment of foci of infection is necessary in treatment of influenzal streptococcic and pneumococcic meningitis.

Every hospital should have a detailed plan of management of all cases of meningitis which the intern can follow. This would undoubtedly reduce the mortality figures.

DISCUSSION

Dr. Joseph C. Yaskin: A striking feature of Dr. Jones's report is that with chemotherapy so many patients with influenzal infections recover. It would be interesting to hear what specific treatment was used for influenzal meningitis. Another point of interest in his study is the high mortality in pneumococcic meningitis. I was under the impression that the mortality was lower. I should like to ask Dr. Jones how often it was necessary to do a mastoidectomy or other gross surgical procedures after the acute stage of the meningitis treated with a sulfonamide compound.

DR. J. ALBRIGHT JONES, Swarthmore, Pa.: I cannot answer that question accurately, because there is no way in which I could get a good follow-up report on these patients. I hoped that Dr. Gammon would be here tonight, for he sees most of the patients, or a large percentage of them, after they leave Children's Hospital, and he could give us an idea as to the number of complications. I should say roughly that few patients with meningococcic meningitis have any complications. In the early days, when treatment was not so good as it is now, probably 1 patient out of 10 had a complication of some kind. There was not 1 case of "chronic meningitis" in this group. Later, some patients reported having headaches or other complications or symptoms associated with more activity at home. Small children cannot tell one much. When, later, they begin to walk, they may have difficulty with locomotion. Our records are not revealing with respect to such complications of convalescence. I omitted the question of complications on purpose, because the patients are so seldom seen by a good neurologist. Most of them did very well, with no complications; so there was no routine examination before discharge.

There is no doubt that the plan of therapy Dr. H. E. Alexander had been using with influenzal meningitis has given the best mortality figures. Her mortality rate was about 20 per cent of 87 cases, which is extremely good.

In cases of pneumococcic and streptococcic meningitis, with which there is usually air-associated infection of the middle ear, mastoidectomy is fairly common, but I cannot state exactly how often it is necessary. Therapy has improved a great deal, and there have been fewer cases of infection of the mastoid in recent years. The whole picture changes as one goes through the records. For example, at Philadelphia General Hospital this year there have been 3 patients with pneumococcic meningitis, all of whom recovered. Only 1 patient recovered in the period from 1938 to 1945.

Paroxysmal Autonomic Crises in Postencephalitic State: Report of a Case. DR. CHARLES I. OLLER.

This paper was published in full, with discussion, in the April 1946 issue of the ARCHIVES, page 388.

Arteriovenous Aneurysm of Great Cerebral Vein and Arteries of Circle of Willis. DR. BERNARD J. ALPERS and DR. FRANCIS M. FORSTER.

This paper was published in full in the September 1945 issue of the ARCHIVES, page 181.

DISCUSSION

DR. CHARLES RUPP: I wonder whether Dr. Alpers has any theories as to the cause of this anomaly.

DR. BERNARD J. ALPERS: Not only do I not have any theories; I do not know how the condition would be identified if it were met again. It is obviously a congenital disorder.

DR. FRANCIS M. FORSTER: Streeter's observations indicate that the great cerebral vein develops some time between the 50 and the 60 mm. stage. Thyng described the appearance of the posterior cerebral artery at the 17.8 mm. stage. It is difficult to understand the development of an arteriovenous aneurysm such as this with such a wide difference in the stages of appearance of its various components.

DR. MILTON K. MEYERS: I should like to ask Dr. Alpers how long this boy had the hydrocephalus.

DR. J. RUDOLPH JAEGER: Dr. Alpers' most interesting case of multiple arteriovenous communications of the cerebral vessels is amazingly similar to the one I reported by title at the Sixty-Third Annual Meeting of the American Neurological Association in June 1937 (*Tr. Am. Neurol. A.* **63**:173, 1937).

My patient was 4 years old at the time of death and had suffered from many attacks of severe nasal hemorrhage, requiring numerous transfusions and nasal packings. The only objective sign of an intracranial lesion was moderate hydrocephalus. Auscultation over the carotid arteries disclosed loud bruits, and palpation revealed thrills over these vessels. An intracranial arteriovenous communication was suspected. Injection of 20 per cent sodium iodide into the left internal carotid artery disclosed that this vessel was so enlarged and tortuous as to be completely looped in the neck. The contrast medium was so diluted, however, by the huge volume of blood passing into the cranial cavity that the details of the anastomosis could not be visualized. Several months later death followed a violent convulsion.

Necropsy disclosed dilated ventricles with probable obstruction of the aqueduct by a huge aneurysm of the straight sinus. Numerous branches of the posterior and middle cerebral arteries had direct communications with many of the central veins of the brain, principally those draining into the straight sinus. Strangely, in both cases examination showed no obvious communications in the anterior cerebral arteries, although it is probable that tiny ones existed. The whole intracranial venous system, including the straight, transverse and sagittal sinuses, were greatly dilated, probably due to arterial pressure inside the venous channels, although this could well have been a part of the congenital malformations.

This case illustrates the fact that nature always repeats its mistakes, no matter how rare they may appear. I well remember Dr. Walter Dandy's comment after he had seen and studied the specimen in my case: "Some day another case with precisely the same deformity will appear." Dr. Alpers' presentation of his case fulfils this prediction.

DR. BERNARD J. ALPERS: The patient had had headaches since he was 6 years of age. His hydrocephalus must have developed after the sutures were closed, for there was no indication of separation of the sutures and no cracked-pot signs were obtained on percussion. The hydrocephalus probably developed simultaneously with the appearance of the headache.

PHILADELPHIA PSYCHIATRIC SOCIETY

O. Spurgeon English, M.D., *Presiding*

Regular Meeting, May 11, 1945

Function of the United States Naval Hospital. COMDR. JOHN M. MCKINNEY (MC), U. S. N. R.

The neuropsychiatric casualty in point of numbers, in point of cost to the Government for future care and in point of rehabilitation and social readjustment is the major problem of military medicine and after the war will become one of the major problems of civilian psychiatry. There are too many of these casualties to be taken care of by federal agencies like the Veterans Bureau. Even if all the psychiatrists in the service were to be turned over to the Veterans Bureau, they could not do the job. Most of these patients must be looked after by civilian agencies and civilian psychiatrists. This is one of the reasons that we on the staff of the United States Naval Hospital here are anxious to present this program to the Philadelphia Psychiatric Society. The neuropsychiatric casualties consist of the psychotic patients, who constitute 1 to 2 per cent of our total admissions; the patients with organic neurologic disorders, consisting mostly of head injuries and peripheral nerve injuries; the psychopathic personalities, the percentage of whom is about the same as that in civilian life, and not an inconsiderable number of patients who are not strictly psychiatric but are the so-called gold-brickers. These men assume symptoms for the purpose of getting out of the service. They are resentful, antagonistic and stubbornly determined to have their way. They do not break the rules, and therefore one cannot punish them. There is no treatment

that seems to have any effect. They will not work, and if they are sent back to duty they report to sick bay the next day with their complaints and continue to do so until they get back on the sick list. Although we may be convinced that they are consciously assuming their symptoms, we cannot prove it. If the man says he has a headache or a backache which is incapacitating, it is impossible to prove that it does not exist. There is only one thing left to do, and that is to get him out of the service on a medical discharge, which, unfortunately, gives him the same type of discharge as the other patients; but this is the best we can do in the circumstances.

By far the greatest percentage of our patients falls into the group with what is known as combat fatigue, or war neurosis. Typically these men, without an actual wound, collapse on the field of battle and are unable to carry on. They either lose consciousness or become dazed and mute and are seized with violent shaking and tremor. They frequently vomit. They may go berserk, start shooting in every direction, begin running either toward or away from the enemy and have to be forcibly restrained. Many men with this acute condition are returned to duty after a few days' treatment in a forward hospital. Those with a more severe disorder are evacuated. It has been my experience that once these patients are evacuated they seldom return to combat duty. Through a series of hospitals, they gradually are transferred back to the states on the sick list and eventually come to such a hospital as this for disposition.

Now, it is easy to serve as a disposition hospital. It is easy to say that this man has been hospitalized for six or seven months, that his condition is not improved, that his symptoms are fixed, that he is of no further use to the service and that his discharge is recommended; but such a system turns out many men on the country who are nervously unsuited to hold a job. They are turned out in such numbers that they cannot be adequately looked after by the Veterans Bureau or by the available psychiatrists in civilian life. We feel that it is our duty to restore to usefulness every one of these men we possibly can, so that they can go back to limited duty or be discharged to civilian life. With this in mind, we treat every patient who shows any possibility of improvement.

In dealing with such a varied personnel we have found it necessary to adopt a number of technics. The officers, by and large, do well with the psychiatric interview and with group psychotherapy. Most enlisted men consider this treatment just so much "bunk," and it not only leaves them cold but annoys them. We have made use, therefore, of every therapeutic means that we could think of and are still looking around for more. We have used suggestion, hypnotism, narcosynthesis and persuasion. We are not unaware of the coexistence of organic diseases in some of these patients, and we make full use of our consultation service with this in mind. Occupational therapy, in all its phases, has been helpful, and this means of treatment is improving and becoming more efficient as time goes on. Each man capable of doing so spends two hours a day on the athletic field. Recently, there has become available to us the rehabilitation work program, whereby jobs in local civilian plants are obtained for these patients while they are still on the sick list. This work is either in the nature of an apprenticeship or along the lines for which the patient's education and former occupation fit him. These patients have all been seen by a Board of Medical Survey, and their separation from the service has been advised. Even though this program has been in use only a short time, its results are most gratifying. These men have their confidence restored; they know they can hold a job; they sleep well without medication; their appetites improve, and their symptoms largely disappear. After a period of work, in which we are assured that the patient can go out and face the world and hold a job, he is given a discharge.

The Psychotic Patient. LIEUT. COMDR. JAMES C. ROBERTSON (MC), U. S. N. R.

The psychotic patients represent a relatively small portion of psychiatric patients seen at this facility and constitute approximately 1.3 per cent of the total psychiatric

monthly census. This figure applies to the psychotic patients who require further institutional care and does not account for the very few such patients who recover to the extent that they may be released from this hospital.

Dementia precox is the most common psychosis, as might be expected. Reactive types of depression and varying degrees of depression accompanying severe war neuroses are observed fairly frequently. Only an occasional patient with manic-depressive psychosis is seen, and paranoid conditions have been extremely rare. Patients with organic psychoses are relatively few, with only an occasional case of psychosis with cerebral arteriosclerosis, toxic psychosis or the psychosis of dementia paralytica.

Patients with mild degrees of depression associated with a psychoneurosis and those with personality disorders of the emotionally unstable, inadequate and constitutional psychopathic inferiority types are often admitted to the psychotic ward, frequently after self infliction of wounds of a superficial character. Many such acts occur during a "panic" reaction and are most often in the nature of a suicidal gesture, consciously motivated, in an effort to escape the unpleasant situation relative to being in the service or in being confined in the brig. These wounds usually consist of several superficial scratches and often occur on one or both wrists. There is a history of the patient's insuring that his behavior was observed before, during or immediately after such an act was committed. The depth of the wound is evidence of the seriousness or lack of seriousness of the attempt, and wounds of more than superficial penetration of the skin are considered evidence of some degree of depression or of a psychosis. The majority of these basic personality disorders, with or without some degree of associated depression, clear up rapidly with hospitalization, sedation and reassurance. As to the disposition of the patient, which constitutes separation from the service: The man who will go to the extent of inflicting a wound on himself, even though it is trivial and used entirely as a means of escape, is considered to have too poorly an integrated personality to adjust to, or to make any satisfactory or dependable contribution to, the service and is better disposed of at the earliest possible moment.

Specialized treatments, such as electric, insulin and metrazol shock, are not carried out on psychotic patients in this hospital. The problem here is for the most part one of disposition, and all men with actual psychoses are transferred to St. Elizabeths Hospital, Washington, D. C., for their further treatment and final disposition. This method of handling the psychotic patients is uniform throughout Naval hospitals. Patients are retained in this hospital only long enough for complete studies, establishment of a diagnosis and estimation of the probable future duration of the psychosis. Those patients who reveal indications of improvement or who have a relatively mild upset and show promise of improvement in a short time without special forms of treatment may be held for several weeks and eventually be discharged from the hospital as recovered.

In addition to the aforementioned patients, many persons with constitutional psychopathic inferiority state, in a prisoner status and awaiting disciplinary action or serving sentence, are seen for evaluation and recommendations as to their future disposition. Discharge from the service is usually recommended. An opinion is necessary as to their mental competence and as to whether disciplinary action and confinement would have a deleterious effect on the patient's mental or physical health.

Neuropsychiatric Casualties Resulting from Exposure to Atmospheric Blast. LIEUT. PEARCE BAILEY (MC), U. S. N. R.

At the beginning of World War I the term "shell shock" was used to describe an unconscious soldier who was found lying uninjured near an exploded shell. By the end of the war this newly coined term had been expanded to include all forms of war neuroses. In World War II attention became centered on the effects of atmospheric blast, largely because of the indiscriminate bombings of dense civilian populations. The term "blast shock," or "blast concussion," was given to the

condition of the unconscious, uninjured soldier who was discovered in the vicinity of a previous explosion.

Whether the effect of a blast in itself can produce cerebral concussion is still controversial. The animal experiments of Denny-Brown and Russell tend to deny that it can. The practical clinical implication of this conclusion is that persons suspected of having a concussion can be immediately transferred to a psychoneurotic classification if it can be demonstrated that their exposure to blast was not followed by secondary impact with a solid surface.

From the standpoint of Naval neuropsychiatry, the nuclear problem in relation to alleged blast experience is the differentiation between a possible resultant post-concussional syndrome and a neurotic complex. For it is on the basis of this differentiation that therapy, prognosis and ultimate disposition depend. As a consequence of explosions, one does see post-traumatic syndromes, purely neurotic manifestations and combinations of the two in varying degrees.

Among several patients observed in this hospital during the last six months, there was only 1 with what we interpreted as a pure concussion. About one eighth of the patients disclosed organic signs with superimposed neurotic manifestations, the former predominating. An equal number showed a combined picture with neurotic elements predominating, and three fourths of the men appeared to have pure neurotic syndromes. Thus, it appears that the commonest disability is pre-eminently psychologic. The most prevalent neurotic reaction was that of anxiety. There was occasional evidence of hysterical fragments, but no obsessive-compulsive states were observed.

In an over-all study of the practical aspects of blast concussion, we believe that a careful evaluation of both organic and psychologic factors is essential. An inclination to declare the condition in any given case as either organic or functional without careful assessment of all values should be discouraged, tempting as it might be. For exposure to blast can cause cerebral concussion either by itself or by hurling the skull against a rigid resistance. But it also can produce panic, which includes a threat to the integrity of the head—probably the most highly prized organ of the body. It can act as a precipitant of a dormant fatigue reaction, or it can activate a previously sublimated neurotic conflict.

In the evaluation of these patients we make a careful search for a history of evidence of surface injury to the head. Prolonged unconsciousness; mental changes, such as confusion, disorientation, retardation and distinct alterations of personality; bloody spinal fluid; abnormal neurologic signs (even though evanescent), focal and general abnormal electroencephalographic phenomena—all are characteristic of altered cerebral economy. Decreased tolerance to alcohol, steady improvement in symptoms and a desire to return to duty also suggest an organic cause. A history of dizziness, increased by postural changes, or inability to concentrate has less diagnostic value. The former is easily elicited by suggestion; the latter is just as common to an anxiety state as to a postconcussional syndrome.

We endeavor not to overlook the possibility of a subdural hematoma or effusion. These lesions frequently show no focal neurologic signs, and papilledema may not be present until late, if at all. A history of head trauma followed by an alternating or shifting state of consciousness with a downhill course should arouse suspicion. Often pneumoencephalographic examination or exploratory trephination is necessary to establish the diagnosis.

From our observations, an inconstant course, extreme variability of symptoms, dramatization and attitudinization, egocentricity and, especially, unwillingness to return to duty favor a psychogenic interpretation. Autonomic instability is common to both types but is usually more erratic and intense in anxiety states. Generalized constriction of the visual fields, diminution of corneal and gag reflexes and a "cloak" of hypalgesia (Foster Kennedy) suggest conversion phenomena. We have found intravenous injection of sodium amytal or pentothal of considerable diagnostic aid. Patients with combat fatigue experience an intense abreaction of battle scenes; psychoneurotic patients are apt to be resistant and argumentative, whereas patients with postconcussional states tend to become confused. Finally,

the use of psychometric tests, particularly those of Rorschach and of the Hartford Retreat, has been helpful in corroborating other signs of transitory mental slowing, which is frequently characteristic of a postconcussional state.

As to therapy, we treat the patients with predominantly organic disturbances by means of a program of rest, assurance and occupational therapy. To patients with postconcussional states who have additional mild symptoms of combat fatigue we offer narcosynthesis and a series of psychiatric interviews. The patients manifesting more chronic personality disturbances are sent for rehabilitation to a convalescent annex of a United States Naval hospital. On the whole the results have been encouraging.

Group Therapy of Combat Fatigue. LIEUT. MANUEL M. PEARSON (MC), U. S. N. R.

Group therapy, largely because there are too many patients and too few psychiatrists, has become an accepted form of psychotherapy in the military services. The method consists of a short talk on a specific subject followed by an open and free discussion. The essential characteristics of each talk should be brevity, simplicity of language, many examples and illustrations of essential points and appropriate questions that are stimulating and thereby control the session.

The group therapy is supplemented by an active daily program consisting of occupational therapy, physical reconditioning and educational measures, such as audiovisual aids in the form of training films, illustrated lectures and short skits. All the accepted methods of individual therapy, such as catharsis, desensitization and reeducation, operate in group therapy. In addition, group identification takes place, attacking specifically one of the chief causes of combat fatigue, that is, breakdown of morale.

In group therapy at the convalescent annex of a United States Naval hospital, an attempt is made to attack the two common denominators of combat fatigue: (1) anxiety, mainly expressed by uncontrollable aggressiveness and bodily symptoms, and (2) depression.

From 45 to 50 per cent of the patients treated in this highly selected group have been returned to duty, mainly to a noncombatant status.

A chart illustrating the entire program for treatment of patients with combat fatigue at this annex was presented.

Combat Fatigue. LIEUT. COMDR. JOSEPH HUGHES (MC), U. S. N. R.

A group of Naval men suffering from combat fatigue was presented. These men were typical cases of combat fatigue as seen in persons who had stable personalities prior to combat. Patients of this type respond favorably to treatment.

CINCINNATI SOCIETY OF NEUROLOGY AND PSYCHIATRY

Charles D. Aring, M.D., *President, in the Chair*

Regular Meeting, Oct. 9, 1945

The Clinical Application of Electroencephalography. DR. GEORGE L. ENGEL.

Since the introduction of the electroencephalograph, some twelve years ago, an enormous amount of data, mostly empiric, has been accumulated in the literature. It seems timely to consider some of the theoretic aspects of electroencephalography and to attempt to derive from them a basis for its application to problems of clinical medicine.

In the final analysis, the electrical activity of the cortex derives from the activity of the individual neurons, the energy for which arises from the intrinsic metabolic activity of the cell (Gerard, R. W.: Factors Influencing Brain Potentials, *Tr. Am. Neurol. A.* **62**:55, 1936). Neuronal potentials may be expected to be

influenced by the following factors: (1) changes in cell metabolism, (2) changes in the electrical properties of the cell membrane, (3) the character of the surrounding fluid medium and (4) influent electrical impulses both independent of and along neural pathways. Changes in rate, form and, within limits, amplitude may be interpreted in part in terms of the individual neuron beat.

However, to account for the rhythmicity and regularity of the electroencephalographic record, some mechanism of synchronizing the individual neuron beats must be assumed. For this a theoretic pace-making system has been postulated, possibly cells the electrical activity of which set other cells off. The more efficient the synchronizing process, the more regular will the record be. Synchrony might then be influenced by (1) the metabolic activity of the pacemaker cells, (2) functional or structural disruption of pacemaker systems and (3) the effect of influent electrical impulses.

A third important factor has to do with the physical properties of oscillating systems (Dawson, C. D., and Walter W. G.: Scope and Limitations of Visual and Automatic Analysis of the Electroencephalogram, *J. Neurol., Neurosurg. & Psychiat.* **7**:119, 1944). With a mixture of different components, important considerations in determining the final complex are: (1) whether the sinusoidal oscillations belong to a harmonic series, (2) to what degree the various components are in phase, (3) whether the amplitude fluctuates rhythmically (modulation) and (4) the algebraic sum of the amplitudes. These considerations are obviously of most importance in circumstances in which there is a mixture of electrically active tissue components or discharging foci.

The normal electroencephalogram has been arrived at by a statistical approach, and there is now fairly general agreement as to its limits. It is influenced by age, by alterations in attention, by reduction in blood sugar and oxygen tension and by numerous drugs that affect cortical activity. In general, hypoxia and hypoglycemia produce progressive slowing and irregularity, and the degree of slowing correlates with the degree of reduction in consciousness. Voluntary hyperventilation produces some degree of slowing in all persons, to a more striking degree in younger subjects, but there is great individual variation. In any one subject the amount of slowing during hyperventilation is increased by (1) lowering blood sugar, (2) lowering oxygen tension of the inspired air and (3) assuming the erect posture. Slowing is always accompanied with some reduction in the level of consciousness.

The abnormal electroencephalogram may be characterized by too slow potentials or too fast potentials or a mixture of the two. These abnormal frequencies may be nonparoxysmal, being continuous in respect to time, or they may be paroxysmal, intruding as it were into an otherwise normal record. In either instance the abnormal frequencies may be generalized or focal.

The nonparoxysmal type of abnormal record is the result basically of disturbances in cerebral metabolism. The prototype of these disturbances is delirium, in which the degree and character of change in the electroencephalogram are more or less independent of the etiologic factor, whether it be anoxia, hypoglycemia, fever, drugs or intracranial disease, but is dependent on (1) the intensity of action of the noxious factor, (2) the acuteness of its action, (3) the duration of its action, (4) the reversibility of its action, (5) the premorbid status of the central nervous system and (6) the relative proportion of uninjured, damaged and destroyed neurons. The more acute and intense the process and the larger the proportion of damaged cells, the greater are the changes likely to be in the direction of slowing and irregularity and the better is the correlation with level of consciousness. The more gradual or chronic the process and the fewer the cells actually damaged at any one time—though there may be many destroyed cells—the less striking are the electroencephalographic changes likely to be, in spite of pronounced disturbances in awareness. These data are based on studies of cases of acute and chronic delirium, dementia, various types of diffuse organic disease of the brain and syncope.

With nonparoxysmal abnormalities of a focal character the same principles hold true, with one important modifying factor, namely, the proximity of the lesion to the nearest electrode and the amount of interposed normal brain tissue. Studies of patients with cerebral vascular lesions—softening, hemorrhage, vasospasm, subdural hematoma—or with cerebral abscess or cerebral tumor provide the data for these conclusions.

The paroxysmal abnormalities are characteristic of epilepsy. The basis of the paroxysmal activity still remains obscure, although it is convenient to think of it as a discharge phenomenon, and as such it is basically different from the nonparoxysmal type of abnormality. Sometimes, however, the discharges may be so frequent or so prolonged as to render differentiations from nonparoxysmal abnormality difficult. In general, our observations amply confirm the data presented in the numerous publications of the Gibbses, Lennox, Jasper, Williams and others. We would emphasize one point, however, namely, the negative diagnostic value of hyperventilation unless a wave and spike pattern is provoked.

In our experience, the electroencephalogram obtained in cases of neuroses, psychoses, psychopathies, alcoholism and behavior problems of childhood is not essentially different from the accepted range of normal patterns when they are properly corrected for age and when epilepsy, organic disease of the brain and the active effects of such factors as trauma, alcohol and drugs are excluded.

This paper was published in full in the March 1946 issue of the *Cincinnati Journal of Medicine,* page 151.

DISCUSSION

DR. MAURICE LEVINE: Have there been any electroencephalographic studies of normal or neurotic subjects in a state of anger or temper or other acute emotion? In the material Dr. Engel mentioned, the patients were in a relatively calm state, were they not?

DR. GEORGE L. ENGEL: Most of the patients reported on in the literature were not watched closely or adequately during the period of study. I know of no specific studies in which that point was investigated. It would be technically very difficult to get records on patients during a display of anger.

DR. MILTON ROSENBAUM: In the group of epileptic patients about 40 per cent had a paroxysmal disorder and 20 per cent had a nonparoxysmal interseizure disorder. I gathered from Dr. Engel's paper that unless there was a paroxysmal disorder he would not make the diagnosis of epilepsy from the electroencephalographic record. On the other hand, it seems to me one has to take into consideration the clinical side of the picture. In other words, if a patient had some sort of spell and a disturbance appeared in the electroencephalogram, either fast or slow nonparoxysmal activity, with no neurologic signs, would Dr. Engel not be inclined to consider that indicative or confirmatory of epilepsy?

DR. GEORGE L. ENGEL: Yes, that is why I am sometimes insistent about not reporting on an electroencephalogram until I get clinical information. If I read a record with wave and spike activity, I am sometimes willing to report it without seeing the protocol. The more precise and accurate the clinical information, the more reliable will be the electroencephalographic interpretation. However, I rarely use the phrase "diagnostic of" in my reports; "suggestive of" or "consistent with" is the more usual expressiion. I usually am still cautious, however, because the requisitions are sometimes hurriedly written and not always accurate. For example, I have sometimes obtained generalized nonparoxysmal, abnormal records from ward patients and have later found that the patient was delirious at the time the record was taken, even though no mention of this was made on the requisition. But I believe that in general Dr. Rosenbaum's statement is correct. The more complete the information is at the time of the tracing, the more reliable is the interpretation.

DR. MILTON ROSENBAUM: I think that clinical judgment probably means more than the interpretation of the electroencephalogram. Dr. Engel did not comment on the 14 per cent of so-called normal people who have abnormal records.

DR. GEORGE L. ENGEL: I did not comment on the 14 per cent who show diffusely moderate slow or fast activity because I am still not sure whether I should consider as abnormal all the records that Gibbs does. I believe my criteria are a little less rigid. Further, I am still not sure that they all mean epilepsy, particularly those with nonparoxysmal activity.

DR. MILTON ROSENBAUM: That is important; it may be that one does not know enough to decide. One of the most interesting contributions made by Gibbs and his group is the idea that these apparently normal persons with abnormal activity are carriers of convulsive disturbance. Much can be built up with this theory in mind, and I wonder what Dr. Engel's own feeling is.

DR. GEORGE L. ENGEL: I think the idea is worth keeping in mind, but I don't think that it has as yet been proved that these people are "carriers," although the data on inheritance are certainly suggestive.

DR. I. ARTHUR MIRSKY: Dr. Engel has emphasized the metabolic aspects of the electroencephalogram and has pointed out that the frequency tends to increase with administration of dextrose to normal persons. Given a patient with delirium who has slow activity, would the activity increase when carbohydrate is administered, as it does in hypoglycemic patients? It seems to me that all the mechanisms that cause slowing of the waves seem, in the final analysis, to be associated with depletion of glucose in the brain.

DR. GEORGE L. ENGEL: My associates and I have not studied the effect of intravenous administration of dextrose on a sufficient number of delirious patients to know whether a slight effect may not be produced in the absence of hypoglycemia. The only group of patients that we have studied carefully is one with Addison's disease. When these patients have hypoglycemia, the administration of dextrose has a specific effect. When the blood sugar is normal, the intravenous administration of dextrose has no effect on the electroencephalogram of patients treated with desoxycorticosterone acetate but does have an effect on the electroencephalogram of patients receiving large quantities of adrenal cortex extract. The few other delirious patients we have studied show no particular response, but this point has not been investigated carefully enough.

I do not believe the data available support the assumption that slow waves are related primarily to depletion of glucose. I suspect that if the respiratory cycle is interrupted at any stage slow waves might result. The barbiturates, for example, interrupt the cycle at the lactic acid–dehydrogenase stage, and high voltage, slow waves result. I do not believe that administration of dextrose will affect this abnormality in the electroencephalogram.

DR. PHILIP PIKER: Clinically, in patients with certain disturbances of lowered awareness the intravenous administration of dextrose seems to have had a beneficial effect, for example, in the aged in the surgical wards who have delirium as a complication of trauma (usually fracture), or perhaps as a result of too much sedation. Patients with barbiturate intoxication often show some response to administration of dextrose in that their level of awareness becomes higher, an observation which would fit in with this notion, too.

DR. GEORGE L. ENGEL: I do not believe that these clinical observations have been adequately controlled with respect to the multiplicity of factors involved. However, they ought to be tested in the laboratory.

DR. I. ARTHUR MIRSKY: What happens in the case of diabetic patients with hyperglycemia but without acidosis?

DR. GEORGE L. ENGEL: We have not studied such patients. I should point out here that oxygen will affect the electroencephalogram in patients without anoxemia. The patient with cardiac disease whose record I showed, gave a striking electroencephalographic response to the administration of oxygen; yet the arterial oxygen saturation prior to therapy was 94 per cent. We have studied a number of patients since and have found that inhalation of 100 per cent oxygen does improve the electroencephalogram even though the patient does not have anoxemia. This is

true in cases of cholemia, uremia and heart failure; so we know a bit more about that than we do about the effect of dextrose.

DR. CHARLES D. ARING: It is interesting that the aged epileptic patient tends to have a normal electroencephalogram. This correlates with what is known about the diminution of seizures with increasing age, an effect which has been attributed to stiffening. It has been supposed that the aging muscles discouraged the exteriorization of the cerebral abnormality. Have any electroencephalographic studies been made in seriatum with increasing age? Have such patients been studied over a number of years?

DR. GEORGE L. ENGEL: I believe such studies have been initiated, but I have never seen any reports. In our experience with children with seizures the records tend to become less abnormal, particularly after the age of 14, but how much is due to decrease in the epileptic factor, how much to maturation and how much to therapy I do not know. It would be difficult to carry out such an experiment, for one would have to get records practically daily in order to control the day to day or week to week variation.

DR. EDGAR L. BRAUNLIN, Dayton, Ohio: What effect would the water-pitressin test have on the electroencephalogram?

DR. GEORGE L. ENGEL: So far as I know such a test has not been made. We tried it once; the patient became delirious before she had a fit. The electroencephalogram showed diffuse abnormality. I do not know how often that occurs.

DR. A. WIKLER, Lexington, Ky.: My colleagues and I at the United States Public Health Service Hospital, Lexington, Ky., have studied the effects of pitressin hydration on the electroencephalograms of drug addicts. None of the subjects was known to have epilepsy. In about one-half the subjects bursts of slow waves were produced by pitressin hydration. Most of those who exhibited paroxysmal slow activity in the record also showed a shift to the slow side of the frequency spectrum. There were a few who showed a shift to the slow side on the spectrum but no paroxysmal slow activity and vice versa. We have not yet tried this test on epileptic patients, but we plan to.

DR. JOHN ROMANO: How many of the subjects had fits?

DR. A. WIKLER, Lexington, Ky.: None of them had fits. One patient was referred to us because of periodic disturbances in behavior. He was considered psychopathic, but it was desired to rule out an epileptic variant. We found nothing abnormal in his routine electroencephalogram but suggested that the pitressin hydration test be made. Such studies were carried out, and a shift to the slow side and paroxysmal slow activity were observed, but abnormal behavior was not produced. Still we were not sure whether these changes were to be considered normal or not; so we made further studies. Now we have the data. Of course, we still do not know whether these changes occur in persons not addicted to drugs, since we have no normal controls. Most of our drug addicts are classified under the head of psychoneurosis or psychopathic personality.

DR. GEORGE L. ENGEL: Did Dr. Wikler study the level of awareness?

DR. A. WIKLER, Lexington, Ky.: There was no gross impairment of the level of awareness. Some of the patients who showed paroxysmal slow activity or a shift in the frequency spectrum were uncomfortable, restless and anxious. Yet they exhibited paroxysmal slow waves. They did not show any evidence of lowering of the level of consciousness.

DR. GEORGE L. ENGEL: My experience in the study of delirium would lead me to suspect that some of these patients described as uncomfortable, restless and anxious would show reduction in awareness if they were tested more precisely. I believe that Dr. Wikler's demonstration of paroxysmal activity during pitressin hydration is of great significance.

Book Reviews

A Future for Preventive Medicine. By Edward J. Stieglitz, M.D., F.A.C.P. Price, $1. Pp. 68. New York: The Commonwealth Fund, 1945.

In the third member of the series of monographs sponsored by the New York Academy of Medicine, Committee on Medicine and the Changing Order, Stieglitz writes a forceful and provocative essay on the changing emphases on preventive medicine. His view of the field is not confined to the activities of health agencies but reaches far into education, research and all the health-building efforts which he terms "constructive medicine."

The main theme of the essay is the need for changing the disproportionate attention, in the present modes of approach, given to the wholesale preventive measures directed against environmental threats. Individualized protection is needed at all ages, whereas at present its use is practically confined to obstetrics and pediatrics. More than one third of the book is taken up by a review, with charts, of the well known changes in vital statistics over the last forty years, the aging of the population due to the successful exploitation of knowledge of bacterial diseases chiefly affecting early life. Emphasis is laid on the increasing burden of the chronic diseases of middle life, leading to the extensive invalidism of the 60's and 70's.

In announcing his program for preventive medicine, Stieglitz, of course, advocated a completion of the mass methods of minimizing health hazards. Extension and coordination of preventive activities by agencies, public and private, is essential. He reminds the reader that the United States is the only senior nation which has no secretary of health but gives cabinet rank to the Postmaster General! But coordination, he says, must be achieved cooperatively, for "a superimposed, centralized, directing authority, such as implied in the Wagner-Murray Bill . . . is almost certain to destroy initiative, suppress imagination and retard progress." A plea is made for a generous expansion of research, supported by tax money, into the causes of degenerative disease. He calls on physicians to come out of their offices and laboratories to lead the fight on ignorance. In schools and colleges, on newspaper and radio staffs, they must see that the public has accurate and not oversimplified information on biologic and health matters.

But his greatest hope for the extension of health, especially in middle and later life, lies in the private, or retail, approach. Fundamental to it is the acceptance of the idea that health is a personal responsibility, a privilege which cannot be granted by any governmental system but earned by only the individual for himself. Stieglitz foresees "well adult clinics" as common as well baby clinics. In office or clinic the patient would receive a "health inventory" and guidance on living habits based on tests of functional capacities.

The author is a gerontologist, mainly concerned with the postponement and control of degenerative disease. In his somewhat austere view of individual preventive medicine, he hardly seems aware of the newer approach which views the individual as inseparable from a family or community setting. "Patients have families"—so do well people. The potential development of child guidance is hardly hinted at, and preventive psychiatry in the preschool years is not mentioned. Nor is marriage counseling noticed.

The sterility of the periodic health examination movement has been due partly to the blindness of its advocates to social and emotional reasons for poor health. Therefore attention might well have been called to the Peckham Health Center, in London, where families had the benefit not only of medical guidance but also of the facilities which made healthy living possible.